

1 placebo responses in each study.

2 You know for instance, if you read Kahn's
3 reviews of the FDA data, he shows that you get all
4 these differences every time you do a study. And so
5 he recommends that you use double blind placebo-
6 controlled studies with randomization.

7 And I really think that that's the kind of
8 standard you generally need for most psychiatric
9 disorders to show that a treatment works.

10 DR. RUDOLPH: Could I respond to that? Or
11 --

12 MEMBER MALONE: You could but I'm not
13 finished yet.

14 DR. RUDOLPH: Okay, sorry.

15 MEMBER MALONE: I also read, you know, the
16 articles that you provided us and this is where -- I
17 mean I had these ideas from other sources but these
18 ideas are also in the articles you gave us.

19 And actually Thase, I think, starts
20 talking about treatment-resistant depression. And
21 even though he gives these rates of zero to ten
22 percent, if you read further in the article, he starts

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1 talking about adjunctive treatments for treatment-
2 resistant depression.

3 And what he does is he starts criticizing
4 studies that don't have randomization and parallel
5 controls. Now I guess -- I mean I wouldn't say that
6 you don't need placebo controls. I think you do.

7 But even if you wanted to argue that you
8 don't need placebo controls, I think he says that you
9 need -- and I believe you need randomization in
10 parallel groups so that, you know, both groups have to
11 be studied out of one study with randomization.

12 And I think this is generally true in
13 psychiatry because of the many unknowns in psychiatric
14 disorders with regard to outcome and treatment
15 response. And I think they dictate that you need a
16 certain type of study in order to show clear evidence
17 of efficacy.

18 I don't know what the tradition in devices
19 but I think that those sorts of standards should be
20 used in looking at studies that are assessing a
21 treatment in a psychiatric disorder.

22 CHAIRPERSON BECKER: Does the sponsor want

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1 to make a response?

2 DR. RUDOLPH: Would you like comment?

3 Most of the literature you cited pertains
4 to more common type depression. And it doesn't
5 necessarily apply to treatment-resistant depression.

6 We'll ask Dr. Rush to comment. One of the
7 citations you gave, the Thase one, Dr. Rush happens to
8 be the second author on that. So he might be
9 particularly appropriate to comment on that.

10 DR. RUSH: That position is known as the
11 senior author in academia.

12 (Laughter.)

13 DR. RUSH: I had to say that.

14 First of all, I agree with your general
15 contention that randomized controlled trials are
16 essential when they can be conducted in a safe and
17 ethical and feasible manner. And when you know that
18 the outcome of the disorder is not uniformly terminal.
19 That is the preferred gold standard.

20 And if I could design a study today, as
21 opposed to what we were working with several years
22 ago, as I mentioned this morning, one can now, given

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1 that we have long-term safety established in this
2 population of very resistant patients with VNS, and
3 that we know effect sizes, we are now in a position
4 that that could be done.

5 The question, I believe, is whether a
6 randomized controlled trial is necessary given the
7 data we have in this condition at this time.

8 So let me expand on that just a little
9 bit. If I could have I think it's 059. It's one of
10 the first slides I had this morning. I just want to
11 go back to that because we discussed an option in
12 there that was very close to I think what is going to
13 be feasible in this population.

14 We -- if the outcome of interest here is
15 long term, which I think it must be given the nature
16 of the treatment that we're dealing with, then we
17 cannot fail to change the treatments in an ongoing way
18 in these patients and hold them on a constant
19 medication regimen for a year. It's not feasible.
20 It's not ethical.

21 I think we'd have -- doctors wouldn't sign
22 up. IRBs wouldn't let us do it. I wouldn't want to

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1 do it. I wouldn't want to be in it. I don't think it
2 should be done.

3 So the only way you can do that is to then
4 allow the treatments to vary individually, being
5 individually managed. And one group that gets VNS and
6 one group that does not get VNS over a long period of
7 time. That is now. It was not feasible then because
8 we didn't have long-term safety. It is feasible now.

9 Even under those conditions, you're going
10 to have an interaction between the treatment, VNS if
11 it is effective and medications and the medication
12 management.

13 In other words, if VNS is being helpful to
14 the medications, the need to change medications will
15 shift. So you'll have fewer medication changes over
16 time in the group that receives VNS as compared to the
17 group that's not receiving VNS.

18 That's actually what we found in the non-
19 randomized comparison, the control, okay?

20 So if you are allowing a concomitant
21 treatment to change while you're giving a fixed
22 treatment to one group and not to the other group, you

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1 are going to have trouble being absolutely positively
2 certain of the level of certainty that we had hoped to
3 get out of the D-01 trial -- sorry, D-02 acute trial,
4 that if the patients differ in outcome, it's all due
5 to VNS because the concomitant treatments are
6 changing.

7 And when you change the concomitant
8 treatments in one group differently than in another
9 group, you have now two confounds. One got VNS, one
10 did not. One had these kinds of changes, one has
11 those kinds of changes.

12 So even there, while you have what I would
13 think would be very strong evidence, you don't have,
14 you know, totally convincing evidence of the type you
15 get with acute ten-week trials of the D-02 acute that
16 we tried to set up.

17 So one final comment. This was actually
18 brought up and debated with -- I think the sponsorship
19 was under the Manic Depressive Association, EGIS,
20 we're talking about studies in bipolar disorders,
21 especially long-term studies.

22 And there was a consensus there that whey

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1 you're dealing with long-term studies in a chronic and
2 recurrent illness, that the feasibility and safety of
3 doing a controlled trial for a long period of time
4 with placebo and fixing all the other regimens is
5 really -- it's just not possible to do that.

6 So because of the extremely depressed,
7 treatment resistant, disabling, lethal nature of the
8 conditions that we're dealing with here, we're dealing
9 in the range of a lymphoma. We're going to lose a
10 certain number of people to this condition in the
11 course of a one-year trial.

12 I mean please go back to the 1,000 people
13 per month with treatment-resistant depression that
14 actually kill themselves. So we're dealing with a
15 really different group. These people are totally
16 ineligible for any pharmaceutical company-sponsored
17 or, by the way, NIH-sponsored trial I've ever been
18 involved in.

19 I am running a sequence treatment
20 alternative to relieve depression trial. That starts
21 with people who are not treatment resistant. They
22 begin with -- citolapram is the first treatment.

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1 They're randomized to four different switch with three
2 different augment treatments as Level 2.

3 If that fails, then they're randomized --
4 still randomized comparison to active switch
5 treatments in Level 3 to active augments in Level 4 to
6 switch treatments.

7 So randomization is possible. But you'd
8 have to start with patients where it is safe,
9 feasible, and ethical. This group has been through
10 really everything. So half have received ECT. If we
11 say well you are in the algorithm that requires ECT,
12 then it would be unethical to give them ECT having
13 already failed on it.

14 So I just -- I need to help you appreciate
15 the nature of the condition which I do think changes
16 the requirements of the trial. Not to come up with
17 any less science than we otherwise can feasibly, we
18 really want to do the best science.

19 But as I walked through this morning, when
20 we were designing the studies and what we knew about
21 the long-term safety of the treatment, in fact the
22 short-term safety to say nothing of the efficacy,

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1 these were the very best trials that we could do.

2 This is the first trial in the D-04, the
3 first time any of these patients at this level of
4 severity have ever been studied at all much less for a
5 year.

6 We didn't know if they would get better,
7 they would get worse. We didn't know how many would
8 kill themselves. We had no idea. No one has ever
9 reported this.

10 And please remember also the adjunctive
11 VNS on to the standard of care, the D-02, you know,
12 post random -- post acute, the long-term D-02. It's
13 the first time, again, anybody had ever studied VNS
14 beyond three months in these kinds of patients in
15 significant numbers.

16 So we were wrestling with a -- really a
17 totally new territory, a terribly difficult illness
18 with a very high risk of disability death, you saw a
19 hospitalization, we had a patient suicide who was a
20 physician and so on.

21 So I think that the question I'm sure for
22 the panel and certainly one I ask myself or I wouldn't

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1 be here is are the data sufficient given what we have
2 to deal with and what we have acquired?

3 Because really any other explanation for a
4 growing long-term benefit, which you don't see
5 following ECT, and you don't see with maintenance
6 medication, you don't see with any long-term
7 treatment, there seems to be at least a sustained, if
8 not growing, long-term benefit in patients who have
9 received VNS at a level of severity and disability so
10 bad that half of the patients receiving ECT in the New
11 York metropolitan area would not qualify for this
12 study. That's the issue, I think.

13 And what more -- what degree of certainty
14 is required given the nature of the condition and the
15 long-term outcome, which grows in benefit rather than
16 wanes, which is true for all other treatments.

17 CHAIRPERSON BECKER: Dr. Ellenberg has a
18 comment.

19 MEMBER ELLENBERG: Can I comment?

20 CHAIRPERSON BECKER: Sure.

21 MEMBER ELLENBERG: I mean if I could
22 follow up on Dr. Malone's question.

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1 CHAIRPERSON BECKER: Actually I think Dr.
2 Malone wanted to follow up on his question.

3 MEMBER ELLENBERG: Oh, I'm sorry.

4 MEMBER MALONE: I think it would be
5 ethical to do another study. First of all, you
6 already did a placebo-controlled study with a sham and
7 it didn't work. So I don't know why it couldn't be
8 done again.

9 And when you did you D-02/D-04
10 comparisons, the response was very quick. So the
11 explanation that you needed more time in the D-02, I
12 mean I don't understand it.

13 The other thing is if you have people
14 going in the D-04 study for one year on treatment as
15 usual, I don't know why part of them couldn't
16 ethically be randomized to an adjunctive treatment.
17 And that you couldn't use some sort of controls in the
18 at least blind assessment of the patients.

19 And I still am not convinced that you
20 can't do those things. And I, myself, do studies in
21 serious psychiatric disorders, too. Currently we're
22 doing studies in autism. And there's no way we could

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1 do drug treatment studies without placebo controls.

2 Now people might argue that autistic
3 children are not going to change much over a short
4 period of time. And they've argued this for OCD and
5 various other psychiatric disorders.

6 But the truth of the matter is that when
7 you do placebo-controlled studies, because of the
8 variability and diversity of response in course for
9 these disorders, you always get responses in all the
10 arms. And you get various responses.

11 And every time you do a study, you get
12 different rates of response. So when you don't have a
13 concurrent control with randomization, I'm not sure
14 what the data means.

15 DR. RUSH: Could I try --

16 CHAIRPERSON BECKER: We should maybe have
17 Dr. Ellenberg's comment and then I'll let you respond.

18 DR. RUSH: Sure, thank you.

19 MEMBER ELLENBERG: Well, Dr. Malone fairly
20 well covered it. But I think in terms of the issue of
21 change of treatments, I just don't see why that is a
22 problem to allow the change of treatments and yet have

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1 as an adjunctive therapy randomized controlled
2 clinical trial an assessment of VNS in the field,
3 randomly assigned to those subjects that are given
4 standard of care is totally analyzable and will give
5 you solid results.

6 So that's just a further comment on what
7 Dr. Malone's point is.

8 CHAIRPERSON BECKER: And actually, before
9 you responded, I come from the cerebral vascular,
10 cardiovascular disease world where that's the norm.
11 You would evaluate if a statin prevents heart disease.

12 These patients are on lots of other therapies. And
13 this is the way the trials are done.

14 It's an add on to all of the other
15 adjunctive therapies that they get so that, again, I
16 think it speaks to the fact that it's not valid to say
17 you can't do the study where medications are changing
18 in the background.

19 DR. RUSH: Well, let me clarify. First of
20 all, that was not my position. So let me be clear.
21 What I was saying was at the time that we started,
22 where we were going we had no evidence of long-term

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1 safety or efficacy of VNS. Could we do a long term --
2 could I have the slide up?

3 Could we do a long-term trial now in which
4 patients are treated with doctors' best choice,
5 severely depressed, and half get VNS and half do not?

6 Yes. Because now we know the long-term safety and
7 have some clue about efficacy of VNS that we didn't
8 know earlier.

9 So I'm saying in the course of
10 development, which I went through this morning when
11 you and I were talking, that was not an option. We
12 couldn't do a long-term. We didn't even have an idea
13 of safety in the short run. No idea that there was a
14 signal at all for antidepressant effect.

15 So I'm not saying that it can't be done.
16 Or it's not ethical or feasible given our current
17 state of knowledge, which has taken six years to
18 acquire.

19 But way back when we started, we didn't
20 have that knowledge base and couldn't, in my view,
21 make that judgment with any evidence, okay?

22 The issue of variable outcome, I want to

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1 have two slides, one is the slide from the ECT
2 followup. Do you know what I'm talking about? The
3 non-responders and responders from the Harold Study.
4 And the other is just the -- I think you have the D-04
5 IDS or something like that. But Harold's is the most
6 important.

7 The fact of the matter is that it is true
8 that patients who enter efficacy trials for depression
9 drug development have a very wide variation in
10 outcome. Placebo responses all over the board.
11 Studies have been done to show that more than half the
12 time the drug doesn't even separate from placebo.

13 What kinds of individuals enter those
14 studies? I've done them for 30 years so I can tell
15 you. And many of you know. You sit on the panels and
16 so on and done the studies. These are individuals who
17 are symptomatic volunteers, taking no other
18 medication, who are willing to go through a drug
19 washout, who are not acutely suicidal, have minimal
20 co-morbidity, psychiatric and/or general medical, are
21 capped at two years in the current episode.

22 Most of the trials in the last ten years

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1 have done that. You cannot be in the episode more
2 than two years. You cannot have failed on more than
3 one medication in the current episode. And they are
4 acute eight- to ten-week trials. And you look for a
5 signal. And they have to accept a placebo
6 randomization, of course.

7 Now that is entirely feasible with
8 symptomatic volunteers. The reason that we did not
9 have a placebo in Star D is because when you move into
10 real patients, and Star D only allows real patients,
11 no symptomatic volunteers, the first thing that you
12 are struck by is massive comorbidity, many of these
13 patients would not be allowed, because of the co-
14 morbid illnesses into the standard efficacy trials
15 with symptomatic volunteers.

16 Second is their length of illness, the
17 length of illness in these patients is on average 20
18 years, the current episode is 20 months. This is a
19 sample drawn out of primary care and specialty care
20 practice. These are real patients, not symptomatic
21 volunteers, okay?

22 More than half the patients in that trial

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1 are not eligible for efficacy trials run right now for
2 the purposes of developing drugs for regulatory
3 approval. That means they're really not
4 representative.

5 We throw out the co-morbid, the general
6 medical conditions, 60 percent have a concomitant
7 general medical condition. May of them are not
8 eligible for placebo-controlled efficacy trials
9 because they don't know the safety of the drug that
10 they're using, they don't want to give it to people at
11 risk, which is very reasonable.

12 So I really -- I must tell you these
13 patients are totally, completely different from
14 patients that go through depression trials. I'm not
15 saying you can't do a randomized trial. I want to be
16 very clear about that.

17 What we know now with this treatment over
18 the long run in terms of safety, you can do a long-
19 term trial. The one thing, though, that you will have
20 naturally is you are going to have to let treatment
21 change over time. You cannot take these people off of
22 all their drugs and make them go onto placebo in my

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1 judgment.

2 No one agree to it. I frankly wouldn't
3 take them off. Many of these patients are in and out
4 of the hospital, barely holding on, with multiple
5 medications to keep them as outpatients. I mean I
6 would -- my IRB would not allow a pure placebo
7 control. I would not do a placebo control.

8 And I don't know a patient, short of
9 psychotic depression, that would take one. But you
10 could do an active treatment, and an active treatment
11 plus VNS. When you -- can I have that slide up?

12 CHAIRPERSON BECKER: And actually we're
13 going to have to kind of curtail your comments a
14 little.

15 DR. RUSH: I'm going to finish -- I'll
16 finish in one minute. Just one slide that says it
17 all. Can I just have that one up that's here?

18 This is the issue of probability of
19 spontaneous improvement in resistant depression. This
20 is a group that received ECT here, okay, and they
21 either did not hit a remission or they did hit
22 remission. This is from a Sackheim study, a Prudic's

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1 study, I'm sorry, of ETC beneficiaries in New York.

2 The people that benefitted from ECT as a
3 group started to lose it, as I showed you this
4 morning, so they worsened. The group that did not
5 benefit or they benefitted but didn't hit remission,
6 they got improvement with ECT but didn't hit
7 remission. Hamilton is now only 20 so they're
8 eligible for studies.

9 Notice their course over the subsequent 24
10 weeks. These patients are not spontaneously
11 improving. Treatment-resistant depression does not
12 spontaneously improve over time as a group. And,
13 therefore, you may not need that kind of control.

14 MEMBER MALONE: Well, I mean it sounds to
15 me like you're saying you're ready to do a pivotal
16 study now you know the parameters. And I still think
17 you need to randomize treatments and have concurrent
18 control.

19 It sounds like you're saying you're ready
20 to do it.

21 CHAIRPERSON BECKER: And I think we're
22 just going to continue to move along and see if Ms.

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1 Wells and Mr. Balo have any specific questions that
2 they need -- they would like to ask.

3 Ms. Wells?

4 MEMBER WELLS: I just have a couple.

5 CHAIRPERSON BECKER: And if I could ask
6 the sponsor to limit their responses to directly
7 answering the question.

8 MEMBER WELLS: The D-03 study is still
9 ongoing?

10 DR. RUDOLPH: That's correct. It's still
11 enrolling patients.

12 MEMBER WELLS: Do you have any
13 intermediate results on that?

14 DR. RUDOLPH: Are you asking about
15 effectiveness? Outcomes? Or --

16 MEMBER WELLS: Yes, effectiveness.

17 DR. RUDOLPH: Yes, we do. The D-02 is an
18 open study so I put that qualification out -- D-03,
19 I'm sorry, is an open study. Their interim results,
20 the results so far are similar to the D-010 in terms
21 of response rates.

22 MEMBER WELLS: Okay. During the D-02, was

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1 it ever suspended by any IRb during the study course
2 for SAEs or AES?

3 DR. RUDOLPH: No, it was not.

4 MEMBER WELLS: Okay.

5 MEMBER BALO: I just have one question.
6 I'm going to give the sponsor a little rest because
7 I'm going to ask the FDA this question.

8 In light of Dr. Davis's information that
9 she put up, there seemed to be a lot of questioning
10 about the propensity analysis and also the covariant
11 analysis. With the data that she put up, I'm
12 wondering if this basically answered some of the
13 concerns that Dr. Lao had, relevant to the propensity
14 analysis.

15 DR. LAO: This is Chang Lao. I see the
16 propensity score repeated measured linear regression
17 analysis which was done reasonably well. But for the
18 comparison of the two response rates, I reviewed it
19 statistic plane everywhere they did talk about
20 logistic regression and covariance.

21 But for some reason, there are many, many
22 different volumes of submissions. To compare two

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1 proportions of response, how come I didn't see this
2 logistic regression and covariance and it means
3 compare two proportions to adjust for covariant. So I
4 would like to know which volume the analysis was
5 there. And that's my concern.

6 MEMBER BALO: But she also provided that
7 they did do adjustment of all the covariance, which
8 was one of your concerns in your presentation. And so
9 I would imagine that that would sort of resolve at
10 least one of the issues you had with your statistics.

11 DR. LAO: Well, propensity score here in
12 the repeated measure and integration includes 17
13 covariates.

14 MEMBER BALO: Yes.

15 DR. LAO: There's three covariates in
16 terms of percentage of the ECT use during the current
17 episode, current use or lifetime use were very highly
18 significant before an adjustment.

19 But after the adjustment, they become non-
20 significantly different between D-02 and D-04. So an
21 adjustment procedure works for the second covariant
22 before an adjustment.

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1 But the reason the propensity score was
2 non-significant in the repeated measured regression,
3 it means after an adjustment they reclassified each
4 individual patient into one of the five subgroups
5 based on the propensity score probability.

6 Like if each individual patient has a
7 predicted probability after D-02 assignment, like you
8 can roughly classify each patient into probability
9 into zero to .2, .2 to .4 and up to .8 and 1.0, rank
10 and order. Then rank and order, then reclassify.

11 So I think that the propensity score did a
12 good job here --

13 MEMBER BALO: Okay.

14 DR. LAO: -- in the repeated measure
15 linear equation.

16 MEMBER BALO: Okay. Thank you.

17 DR. LAO: Thank you.

18 MEMBER BALO: Dr. Pena, can I ask you a
19 question?

20 I'm just wondering with D-04, you know,
21 dealing with the sponsor why there was never
22 discussion about safety data.

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1 DR. PENA: In D-04?

2 MEMBER BALO: D-04.

3 DR. PENA: Okay.

4 MEMBER BALO: I was wondering in your
5 discussions with the sponsor when they were submitting
6 D-04, did the FDA ever request them to have safety
7 data?

8 DR. PENA: The D-04 was conducted local
9 IRB jurisdiction so it didn't require any FDA
10 approval. In addition, when they submitted the
11 revised statistical plan back on September 3, 2002,
12 FDA responded with a correspondence letter saying that
13 we had serious concerns with this comparison.

14 We additionally had conference calls that
15 further underscored those concerns. So I think we had
16 a lot of concerns about that comparison and use of
17 that open label controlled study, observational
18 controlled study.

19 MEMBER BALO: Okay, thank you.

20 CHAIRPERSON BECKER: Dr. Witten, do you
21 have any comments or questions?

22 DR. WITTEN: No.

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1 CHAIRPERSON BECKER: And I think that
2 before we move on, Dr. Fochtmann has three questions
3 that she would like to address to the person
4 responsible for safety issues.

5 MEMBER FOCHTMANN: The first question that
6 I have -- actually the first two questions, I believe
7 on the exclusion criteria for the study, was mentioned
8 patients with carotid stenosis as shown by ultrasound
9 and the other group of patients that was mentioned
10 were patients with a diagnosis of obstructive sleep
11 apnea because of the chance of increasing apneic
12 episodes with the stimulation.

13 My question relates to whether there is a
14 need for either initial specific screening for those
15 disorders in people who would be using this clinically
16 and/or ongoing assessments? Certainly, I know,
17 obstructive sleep apnea is often undiagnosed in
18 community samples and in a group such is this which,
19 as your data show, have an increased body mass index,
20 there might also be further increases in sleep apnea.

21 So is that something that needs to be
22 taken into consideration from a safety standpoint in

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1 terms of future use in the general population?

2 DR. RUDOLPH: There is already a warning
3 in our labeling with regard to obstructive sleep
4 apnea. It doesn't require screening of the patient,
5 however. And we have the epilepsy safety experience
6 which shows that that warning -- it would suggest that
7 warning has been sufficient to protect the safety of
8 the populous.

9 MEMBER FOCHTMANN: Okay. But warning
10 specifically relates to diagnosed sleep apnea. And my
11 concern is about people who may have it that are just
12 not diagnosed.

13 DR. RUDOLPH: No, I understand. And
14 that's how the warning is currently written in the
15 label.

16 MEMBER FOCHTMANN: Okay. The other
17 question that I had related to the issue of patients
18 who are not adherent with treatment. And it was
19 specifically mentioned both in the presentation and
20 the graph labeling information that this might be a
21 particular treatment that could be considered in
22 patients who are non-adherent.

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1 My concern with that relates to the issue
2 that the patient brochure and some of the other
3 information in the volumes we received mentions the
4 need for individuals to continuously carry the magnet
5 with them in the event that the needed to turn off the
6 stimulation.

7 In a patient who we would see clinically
8 that we would think may not be totally reliable and,
9 therefore, non-adherent, would we have reason to be
10 concerned about their reliability in not always
11 carrying the magnet with them from a safety
12 standpoint?

13 DR. RUDOLPH: The magnet is mostly a
14 convenience for temporarily turning off stimulation
15 for minor side effects like a common situation where
16 it's used in turning off stimulation to stop voice
17 alteration in a patient who might sing in a choir or
18 who has to do public speaking. So it's there more for
19 these nuisance side effects. And it doesn't, you
20 know, the absence of carrying the magnet wouldn't
21 impose any undue major safety risk on the patient,
22 which, I think, is a short answer to your question.

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1 DR. RUSH: There's just -- there's a
2 little convenience factor, in order for the magnet to
3 stop the stimulation, it has to be held over the
4 device.

5 So you'd have to intentionally tape the
6 magnet over the device and walk around with that taped
7 on 24/7 in order to stop the device. So the
8 likelihood in our clinical experience is that really
9 is not likely at all.

10 MEMBER FOCHTMANN: Yes. My concern was
11 more that there would be an adverse event. That the
12 patient would have left the magnet at home. And they
13 wouldn't be able to turn it off.

14 DR. RUSH: Oh, we've had some patients ask
15 -- yes, we've actually given patients several magnets.
16 One for the car, one for the office, and one for
17 home. Several of our patients actually like that.

18 MEMBER FOCHTMANN: Okay.

19 CHAIRPERSON BECKER: Another question
20 here.

21 MEMBER JAYAM-TROUTH: I had actually a
22 couple of questions.

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1 Does it effect it when you go through the
2 airport screening process you know?

3 DR. RUDOLPH: No.

4 MEMBER JAYAM-TROUTH: There's no magnetic
5 interference then?

6 DR. RUDOLPH: No.

7 MEMBER JAYAM-TROUTH: So you don't have to
8 readjust it or reset it?

9 DR. RUDOLPH: No.

10 MEMBER JAYAM-TROUTH: What about this
11 imaging? You know I was just looking at those and I
12 was a little puzzled. And apparently all of the
13 stimulation on the PET scan appears to go to the left
14 brain? You know is that then true that the major
15 connection is to the left brain except the single
16 place where it crosses over and goes to the right
17 brain?

18 DR. HENRY: Yes, Thomas Henry, Associate
19 Professor of Neurology, Emory University. I would
20 like to disclose that I did imaging studies. And
21 Emory was reimbursed by Cyberonics as well as my
22 participation in the epilepsy E-05 study. And my

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1 transportation to this meeting was paid.

2 If I could have the PET slide that is in
3 question here. I think this is --

4 MEMBER JAYAM-TROUTH: 38.

5 DR. HENRY: Well, this one.

6 MEMBER JAYAM-TROUTH: Slide 38.

7 DR. HENRY: Oh, slide 38, okay.

8 I'm not sure that this is the slide you're
9 looking for. This is one that address your question
10 showing that acutely during vagus nerve stimulation
11 there are significant blood flow increases bilaterally
12 as well as some significant blood flow decreases.

13 This is a group of five patients in the
14 epilepsy E-05 study who were scanned within the first
15 24 hours after VNS was turned on for the first time.
16 So this is an acute stimulation effect. PET scans
17 were compared during vagus nerve stimulation versus
18 without stimulation within subjects and then co-
19 registered to MRI here across five subjects.

20 So with one centimeter spacing on these
21 axial images, subject left on image right, the usual
22 convention, we were able to discern areas of

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1 significant blood flow increase in the dorsal rostrum.

2 The medulla -- here are other brain stem regions
3 along known pathways projecting up to autonomic and
4 limbic centers in the hypothalamus, the thalamus
5 bilaterally.

6 And then bilateral orbital frontal cortex,
7 insular cortex, and other relevant areas of the limbic
8 system. Or posteriorly, however, in the singlet and
9 hippocampus decreases were seen, the main area of
10 significant asymmetry is in the subjects who felt left
11 cervical paresthesias during stimulation.

12 Only the right sensory strip, precentral
13 gyrus was really activated. And you can see a
14 specificity there for this somatasensory distribution
15 here just on one side.

16 But most of the other stimulations may
17 have been a little asymmetric but overall were
18 bilateral.

19 I hope that addressed your question.

20 MEMBER JAYAM-TROUTH: Well, yes, but your
21 PET Scan No. 38, you know, in your slides was almost
22 lateralized to the left side.

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1 DR. BRANNAN: This is the image you were
2 asking about, is that correct?

3 MEMBER JAYA-TROUTH: Yes.

4 DR. BRANNAN: Okay. Also get ready for
5 the next slide, 39 -- not this one but the next in the
6 sequence.

7 In this particular -- when you're looking
8 here, you actually see a lot of midline activity in
9 the singlet but you do see in these particular slices
10 activity on the left. But when you're looking at one
11 slice, you're not looking at the whole brain.

12 And so similar to what Dr. Henry was
13 saying, 052 please, 052, slide up, here, I think, this
14 is one-year scan data that is available from
15 University of Minnesota. And let me just draw your
16 attention -- let see -- right down here, so you see
17 very nicely there's bilateral, almost mirrorlike
18 activation or deactivation patterns here.

19 So there's really bilateral activation.
20 It doesn't mean that there aren't some areas that are
21 asymmetric but you're not seeing left-sided activation
22 in the PET studies or FMRI studies either.

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1 CHAIRPERSON BECKER: Thank you.

2 MEMBER JAYAM-TROUTH: Thank you.

3 CHAIRPERSON BECKER: In the interest of
4 time, we're going to move on to the FDA questions.
5 And do you want to put the FDA questions up for us?

6 I think the first question that the FDA
7 has is one that we've spent a lot of time discussing
8 already, and that's the limitation of the long-term D-
9 02/D-04 comparative analysis.

10 And that the comparisons are not from a
11 randomized data set but rather comparison of outcomes
12 from an investigational device study and observational
13 control study.

14 And while the sponsors did do a propensity
15 adjustment strategy, there are still potential biases
16 that exist.

17 And so the FDA would like the panel to
18 discuss the impact of a comparative analysis of non-
19 randomized subject data, comparison of outcomes from
20 an investigational study and the observational study
21 and the unmeasured patient variables upon efficacy
22 outcomes in this PMA submission.

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1 And I think we'll just go around the table
2 and get comments from the different panel members.
3 And we'll start with Dr. Ellenberg.

4 MEMBER ELLENBERG: This is a non-
5 randomized comparative controlled trial with a single
6 blind on the primary outcome measure. And in my view,
7 in spite of the extraordinary analyses presented by
8 the sponsor, attempting to demonstrate that the
9 baseline observed differences and other
10 characteristics that might effect the nature of the
11 patients that were entered into the two arms, that
12 this type of analysis by showing that there were no
13 difference -- there were differences seen, either
14 clinically or statistically, does not replace the
15 concept for randomization.

16 And it does not specifically address the
17 issue of all of those variables that we cannot
18 measure, did not think about, and come into play when
19 you compare two arms as has been done here.

20 And so my sense is that we need to stick
21 to the standard of a randomized controlled trial in
22 order to evaluate the VNS. And that's a set standard.

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1 It appears from the discussions we've had with
2 sponsor that such a trial could be done today although
3 it couldn't be done perhaps at the time that the
4 original D-02 was done.

5 So my conclusion is that there could be a
6 major impact on these results that we cannot see, we
7 cannot measure. And we can guess all we want. We can
8 speculate. But I don't find this at the acceptable
9 level of a randomized clinical trial.

10 MEMBER JAYAM-TROUTH: While I agree that
11 there is a problem there, and that we do have, you
12 know, no definite randomized trial here, there's no
13 comparison, but I do see the point that, you know, at
14 the time that this was taking place, such a
15 randomization could not have occurred.

16 You know I also feel that when I look at
17 the two groups of people and I look at the D-04 and
18 the D-02, that the D-04 certainly had, perhaps, you
19 know, patients who were better. You know from the
20 slides that we can see, they did not need as much ECT.

21 And they, you know, had not been into as many
22 multiple trials, et cetera, you know, as the patients

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1 who were put into the D-02 studies.

2 So I think that even though these are not
3 really truly comparable, I think that, you know,
4 having used it as data for comparison, even though it
5 doesn't fit into randomization, I feel that, you know,
6 at the time that this was a study that we could kind
7 of look at and we could say, okay, you know, there is
8 a comparison there that can be made.

9 If at all, it's skewed towards worse
10 patients in the D-02 study.

11 CHAIRPERSON BECKER: Dr. Fochtman?

12 MEMBER FOCHTMANN: I would certainly
13 concur with both of those impressions. And I would
14 also really emphasize the point that has been made by
15 the sponsor that this compared to studies of depressed
16 patients in other studies is a very, very unique group
17 of individuals.

18 And one of the groups of patients that we
19 as clinicians, even those of us who have expertise in
20 treatment such as electroconvulsive therapy, are
21 always confronted with how to assist these individuals
22 with these obviously devastating illnesses.

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1 And so although I would agree that in an
2 ideal world it would be nice to be able to do, at this
3 point knowing what we know now, further study, I'm
4 concerned about the potential burden to patients who
5 might not be able to receive a viable treatment for
6 this very severe illness.

7 And so I would want to seriously weigh
8 both sides of the issue.

9 CHAIRPERSON BECKER: I would just add that
10 I think the data look very promising and do suggest
11 that there's a benefit there although it's really
12 difficult to be sure given the difficulty in comparing
13 the two groups.

14 And this seems like to me the right time
15 to do the pivotal control trial.

16 Dr. Wang?

17 MEMBER WANG: Yes, just sort of echoing
18 what I said earlier, in terms of the fact that you
19 didn't see differences after, you know, before versus
20 after your propensity score adjustment, there's
21 several ways to interpret that. One is, you know,
22 maybe you didn't have a very good propensity score.

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1 You know you didn't either have the unmeasured
2 variables that you needed.

3 There are other ways that you can also
4 have a poorly performing score, you know, how did you
5 categorize your variables? What did you do with your
6 missing information? You know did you bury it into
7 the extremes? That sort of thing.

8 But what I do find promising is your acute
9 phase data which is randomized. And maybe this is a
10 point for later discussion but I'm just curious why
11 there wasn't sort of a push to do more -- not as Dr.
12 Rush was saying long term but acute phase randomized.

13 Why not acquire more of that data?
14 Because it looked like you were about on the threshold
15 of seeing a significant result.

16 DR. JENSEN: I sympathize with your
17 situation. As an interventional nerve radiologist, I
18 deal with a lot of groups of patients who have no
19 other viable alternatives except what is being
20 offered. I liken this particular situation with ours
21 concerning percutaneous vertebroplasty, which is a
22 treatment of patients with osteopartic compression

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1 fractures who have failed all medical therapies.

2 And what we found was that there was a
3 very high response. But when we started out with
4 this, we didn't do a randomized control trial. We did
5 best medical therapy versus vertebroplasty with using
6 patients as their own internal controls.

7 When we then went back and tried to do a
8 randomized controlled trial to show the data, it was
9 impossible because vertebroplasty was now too
10 widespread. It was available everywhere. And
11 patients would not consent to being randomized.

12 So for me one of the issues is of timing.

13 One of the differences between this particular study
14 and vertebroplasty is we had consistently across
15 different sites 80 to 90 percent response. And yours
16 is 30 percent.

17 So for me one of the issues is timing.
18 This may be the only time to actually get the data
19 that you need to prove without some of the doubts that
20 have been raised here that this is truly efficacious.

21 MEMBER ORTIZ: I agree with what's been
22 previously said that it's unfortunate this wasn't

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1 designed differently but I think it's understandable
2 given the nature of this group, that the blinding that
3 was built into this study.

4 And my impression is that both the
5 anecdotal reports as well as the long-term symptom
6 reports and the comparison with the K-04 group
7 suggests that this would provide a significant
8 alternative treatment to what's available.

9 CHAIRPERSON BECKER: Dr. Malone?

10 MEMBER MALONE: I guess I already said
11 that I don't think that you can use that sort of
12 control. I think that the sponsor did demonstrate
13 they could randomize to a sham treatment and carry out
14 such a study. You know I think that's what's needed.

15 It is possible that this is a viable
16 treatment. But it's also possible that it's not a
17 treatment. And there are ethical issues on both sides
18 of the fence here.

19 So I'm not sure that it's quite ethical to
20 give a treatment for which there is not, I don't
21 think, substantial treatment. You may just be
22 providing people with more side effects and no

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1 increased efficacy.

2 And, you know, there's something I don't
3 think the PA analyses can ever get out, when we do our
4 studies, we screen people for studies. And once they
5 find out it's a drug study, there are people, and we
6 never can predict from any demographics, who say no, I
7 don't want my child on a drug.

8 I only have to think that the group of
9 patients who will consent to have this procedure done,
10 because I don't think it's -- it's not getting your
11 tooth pulled, is different in some way that we can't
12 really find in these PA analyses.

13 And so I think, you know I think that's
14 the failure of those analyses, that you may be pulling
15 different groups of patients because of the
16 interventions. Some people will agree to some
17 interventions and some won't.

18 And there's no way from the data that I've
19 seen that you can tell who would or wouldn't agree.

20 CHAIRPERSON BECKER: Ms. Wells?

21 MEMBER WELLS: I agree with Dr. Ortiz.

22 CHAIRPERSON BECKER: Mr. Balo?

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1 MEMBER BALO: I think we've heard a lot
2 about the design of the study, whether it's randomized
3 or non-randomized. And I think the company really --
4 I think Dr. Rush really explained it pretty explicitly
5 about they really didn't know what they had when they
6 started the study. It was never really a long-term
7 test for this population that was so unique that we
8 didn't know how the VNS was going to operate.

9 I think from a randomization perspective,
10 I think in devices, sometimes randomization studies
11 are not done and devices get approved. Obviously the
12 optimal would be do randomization.

13 But my feeling is that the company
14 actually went out, dealt with the FDA, looked at the
15 data after three months, saw that they needed to get
16 some long-term results because they -- and I think I
17 also agree with Dr. Wang that, you know, the acute
18 data did have some promise to it.

19 And I do feel that maybe if they would
20 have continued with this study a little bit longer, it
21 would have given them a little bit better data. And
22 we wouldn't be in such a controversy right now.

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1 But I do also feel that the analysis that
2 was done by Dr. Rush and by the sponsor did try to
3 show that there was some potential benefit. And I do
4 feel that there is some potential benefit to the
5 device.

6 CHAIRPERSON BECKER: So it sounds like the
7 panel thinks that the sponsor did a really good job in
8 dealing with the data that they had. But the data
9 that they had was not the optimal data. And that
10 there are limitations in comparing the two groups that
11 exist.

12 DR. WITTEN: Thank you.

13 CHAIRPERSON BECKER: Next we'll move on to
14 question 2 which is the sponsor believes that D-02
15 long-term outcomes are not due to a placebo effect.
16 The data provided in the PMA includes a placebo effect
17 rate, 20 percent, in sham treatment controlled
18 subjects at acute phase exit as defined by HAM-D score
19 less than 18.

20 Patient expectation of participating in an
21 investigational study for new therapies, such as the
22 D-02 study, may have also been greater than the

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1 expectation of participating in an observational
2 control study.

3 Please discuss the placebo effect and
4 impact upon clinical outcomes presented in the PMA.

5 And I think, Mr. Balo, we're going to
6 start at your end of the table and come around this
7 way.

8 MR. BALO: I have no comment about that.

9 CHAIRPERSON BECKER: Ms. Wells?

10 MEMBER WELLS: I have no comment either.

11 CHAIRPERSON BECKER: Dr. Malone?

12 MEMBER MALONE: As I said before, when
13 Khan reviewed all the FDA data and I know that Dr.
14 Rush doesn't think it applies but I think some of it
15 has to apply. It's the best data that we have.

16 The placebo response rates are different
17 in every study. And so I think that it's hard to
18 really know what the -- what placebo response there is
19 in this study.

20 The other thing is when Khan examined all
21 of the FDA data -- well, I don't know if it was all,
22 it was a ten-year period of recent antidepressant

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1 trials, and there have been a lot of them recently,
2 what he found was that the HAM-D scores decreased for
3 every group. So they decreased for the drug treatment
4 group. They decreased for the drug comparator group.
5 And they decreased for the placebo group.

6 So when you have a long-term study and you
7 get a decrease in scores, it's really hard to know
8 what that means. One would actually expect scores to
9 decrease in the long term. So that, for instance,
10 when the scores decrease across time in D-02, it's
11 hard to know why that happens without what I would
12 think would be an adequate comparator.

13 CHAIRPERSON BECKER: Dr. Ortiz?

14 MEMBER ORTIZ: I guess my only comment is
15 that psychiatric studies placebo responses are often
16 high. And I think this particular population is so
17 complicated and probably does have a very high
18 incidence of Axis 2. It's hard to interpret the
19 placebo response.

20 CHAIRPERSON BECKER: Dr. Jensen?

21 DR. JENSEN: I agree with Dr. Ortiz. I do
22 appreciate the sponsors pointing out though that

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1 placebo response is normally short and not long term,
2 which is certainly what we saw with vertebroplasty,
3 too. Patients would get better immediately and then
4 go back to having chronic pain.

5 I think another big confounding factor for
6 me is is that it's very difficult to blind this study
7 because I think a lot of patients probably knew
8 whether or not they actually had the device turned on.

9 And so for me that confounds what the placebo effect
10 might have been.

11 MEMBER WANG: Yes, I think this is another
12 one of those issues where it's probably -- there is
13 something probably still there despite the very sort
14 of rigorous reassurances, including the fact that in
15 the acute phase, there was, you know, 11 percent of
16 people responded to the sham treatment.

17 The -- I'm still curious, though, earlier
18 I raised this issue about sort of the IDS, the
19 difference in the outcomes when you look at the IDS
20 versus the HAM-D which the HAM-D is, we think, is the
21 gold standard. But we see that the responses were
22 somewhat, you know, more robust at the IDS.

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1 And I'm wondering is it that the IDS is
2 more prone to -- because it's a self report and not a
3 clinician-administered instrument, is it more prone to
4 placebo effects or, you know, other kinds of
5 information biases? Because it may be a more relevant
6 measure for depression than the maybe antiquated HAM-
7 D.

8 CHAIRPERSON BECKER: I suspect that many
9 of the benefits seen of vigorous stimulation in the
10 study were related to the placebo effect but not all.

11 And part of me wants to say well, so what if it was a
12 placebo effect? This is a very treatment resistant
13 group of patients.

14 And if this placebo effect works for them
15 and others didn't, that should be fine. But I think
16 there's enough safety concerns with the device,
17 especially as brought up by Dr. Jensen with the young
18 patients who are being implanted now are going to have
19 these devices in for a very long period of time, that
20 we really do need to be sure that the effect is more
21 than placebo.

22 And I think only a true randomized

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1 controlled trial is going to answer that for us.

2 MEMBER FOCHTMANN: I certainly would
3 concur with the concern about the difficulty in
4 interpreting any sort of placebo effect. I believe
5 one of the previous presenters emphasized the
6 difference between a placebo effect and an actual
7 response as measured by rigorous definitions of the
8 term response. And also persistent response.

9 And I think that those are three very
10 different parameters that should be considered
11 independently.

12 I'm also concerned about the short term,
13 the blinding in the short-term study as well. But I'm
14 not sure, given the nature of the treatment, how one
15 could adequately prevent people from knowing or
16 prevent the investigators from knowing based on the
17 fact that the side effects seem to be at least in some
18 instances dose related, related to the stimulant's
19 intensity.

20 I'm not sure how you could design a study
21 that would totally blind those effects.

22 MEMBER JAYAM-TROUTH: I agree that yes, I

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1 mean there's really nothing in the acute phase that
2 separated the two groups, you know the sham as well as
3 the D-02 groups.

4 But my own feeling is that this is an
5 invasive procedure. You know people are looking for
6 something to happen. And then you're coming there and
7 stimulating them almost every four hours, every day.
8 They don't know that they're getting stimulated.

9 And I think that in itself probably set
10 off, you know, neuro epinephrines and every other
11 agent inside the brain and I think, you know, that
12 type of an invasive process possibly is responsible,
13 you know, that term, that 12-week term probably was
14 not enough, you know?

15 And possibly if that sham period had
16 continued a little longer, we might have seen a
17 difference. But since the study was not set up to
18 show that, we do definitely see a difference in the
19 long-term study. And it seems like it is a
20 consistent, it is a sustained difference.

21 And even though I agree that this was
22 definitely the sham in the acute phase in the D-02 did

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1 not show, you know, any significance, I think the
2 long-term studies kind of outweigh that.

3 MEMBER ELLENBERG: I concur with Dr.
4 Becker.

5 CHAIRPERSON BECKER: So Dr. Witten, it
6 sounds like the panel, in general, feels that without
7 a randomized study, it's very difficult to know what
8 to make of the placebo response and how much of the
9 response of VNS stimulation is due to the placebo
10 response.

11 Although there seems to be some general
12 belief that there probably is an effect that isn't
13 completely placebo related, we just don't know how to
14 measure that at this point.

15 So the third question that the FDA has
16 posed has to do with concomitant medications in ECT
17 use, which were not standardized in either the D-02
18 long-term study or the D-04 observational controlled
19 study.

20 So please discuss the impact of
21 concomitant medications in ECT use on interpretation
22 of the efficacy of VNS therapy for treatment-resistant

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1 depression.

2 And we'll start with Dr. Ellenberg this
3 time.

4 MEMBER ELLENBERG: Well, this certainly
5 proved to be a very interesting issue. And again I
6 think the sponsor did an extremely nice job in trying
7 to tease out the impact of concomitant meds.

8 I would agree or I am sensitive to the
9 comment that Dr. Wang made that it's difficult to sort
10 of speculate when there is a change in medications and
11 you start dealing with less observation carried
12 forward or dropping medications or other forms of
13 censoring, it's very difficult to speculate as to what
14 that means in terms of the outcome.

15 I would find it difficult to argue that
16 because the average time to change the medications for
17 the DOT group, the combined DOT group with the
18 immediate and delayed start of VNS, that that group
19 was disadvantaged in the sense that they only had
20 seven months of treatment rather than the full year.
21 It's not clear to me that one can speculate on that.

22 Some additional things that I would like

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1 to see, which I couldn't find in the volumes, would be
2 the distribution of the change of medication times for
3 those on the DOT component rather than just the
4 average. And that might help us to better understand
5 the impact on the analysis.

6 The second point, again I think this came
7 out of Dr. Wang's questioning, but when the chart was
8 put up for the slope coefficients, looking at, I
9 believe, five different types of censoring, it seems
10 to me that there were dramatic changes in the slopes
11 presented with the different types of censoring.

12 And if you disregard the issues of
13 statistical significance, that sensitivity analysis,
14 to me, was screaming that this whole process is not
15 robust to changes in the definition of how you censor
16 or how you treat the censoring in the analysis.

17 So I think this is a question that needs
18 further study. And it's certainly very interesting.

19 CHAIRPERSON BECKER: Thank you.

20 MEMBER JAYAM-TROUTH: The way I see it,
21 you know, even if you did have, you know, ECT
22 interfering and people could change ECT anytime they

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1 wanted, they could change their medications anytime
2 they wanted, I mean there was really no randomization,
3 there was no algorithm.

4 And I guess it's the nature of the
5 treatment that's the nature of the disease. But if it
6 was skewed, it was skewed towards, you know, the D-02
7 actually having worse patients, you know, and patients
8 who had had to seek more ECT, you know, as compared to
9 the D-04s.

10 And I think that the fact that they needed
11 much less medication adjustment, you know, I think
12 does go along with, you know, that there was some
13 effect in there. So to me I think that even though
14 there was no definite data that you could compare and
15 there was a lot of alterations being made, if at all,
16 it went skewed towards the D-02 study.

17 CHAIRPERSON BECKER: Dr. Fochtmann?

18 MEMBER FOCHTMANN: The issue of the
19 concomitant medications is one that I continue to have
20 questions about, the issues that I raised earlier,
21 which were answered, but also because of the opposite
22 side, and that is could concomitant medications be

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1 influencing the efficacy of VNS, specifically the
2 medications with anticonvulsant properties, given what
3 we know about ECT efficacy being impaired, in some
4 instances, by a medication such as benzodiazepines.

5 And so I think that without some attempt
6 at standardizing some of the concomitant medications,
7 it's difficult to know how to interpret one way or
8 another what impact that the medications might have on
9 the VNS efficacy.

10 The other issue is just in terms of the
11 wide variety and the number of medications that people
12 were taking concomitantly, which makes it difficult to
13 know how to interpret. You could argue that because
14 there was -- that was present in both groups that it
15 should wash out across the groups but, again, it's
16 hard to know.

17 But at the same time, hard to make a
18 standardization given the number of failed trials that
19 these individuals had already experienced.

20 CHAIRPERSON BECKER: I have nothing to
21 add.

22 MEMBER WANG: I think this issue, you

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1 know, allowing changes in the concomitant treatment
2 makes this data we're actually looking at not the
3 efficacy of a device but we're now looking at the
4 efficacy of sort of strategies, you know, and it
5 really is hard to sort out because, well, for that
6 reason.

7 And, again, as has been sort of raised
8 again, this issue of the reduction in the magnitude of
9 the effects estimate after you censor people who made
10 changes or, you know, added ECT or that sort of thing,
11 suggests that the rescue treatment may have been more
12 robust, you know, a good rescue treatment. And maybe
13 that is partially explaining the efficacy.

14 But on the other hand, what makes you
15 analyses that you showed us conservative is the whole
16 issue of ceiling effects. I wonder to the extent to
17 which, you know, the fact that you allowed everyone to
18 be on concomitant treatments, did they max out and are
19 you not able to see sort of efficacy because everyone
20 is on, you know, good regimens potentially.

21 DR. JENSEN: I agree with Dr. Wang.

22 MEMBER ORTIZ: My comment about this would

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1 be that it would be helpful, I would think, to get
2 further information both about the types of ECT, at
3 what point it was used, the specifics of
4 antidepressants.

5 As Dr. Fochtmann was saying, some of the
6 antipsychotic medicines actually lower the seizure
7 threshold as well as does bupropion. And again those
8 kinds of issues I think will be very important for
9 clinicians to understand better because I think though
10 the request is only for the VNS, the reality is
11 clinicians will be combining it.

12 And the more information they have the
13 better.

14 CHAIRPERSON BECKER: Dr. Malone?

15 MEMBER MALONE: I agree that it's
16 difficult to know the effect of the concomitant
17 medicines in ECT. I don't know if there's any way a
18 round having this. It could maybe be more
19 standardized in a protocol.

20 But I think obviously it would have some
21 effect on the outcomes.

22 CHAIRPERSON BECKER: Ms. Wells?

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1 MEMBER WELLS: I have no comment.

2 CHAIRPERSON BECKER: Mr. Balo:

3 MR. BALO: I just think, you know, like
4 everybody said, it's going to be pretty difficult. It
5 seems like this is a very difficult patient population
6 and the amount of ECTs or the amount of different
7 medications they take would be very difficult to sort
8 out.

9 And I think the sponsor has really done --
10 at least like Dr. Ellenberg said, teased out as much
11 as they could from the study that they did.

12 CHAIRPERSON BECKER: So in summary, it
13 sounds like the panel believes that because this
14 wasn't the randomized trial, it's hard to know what to
15 make of the concomitant medications, especially in
16 light of the fact that there's no standardized
17 approach to medically treating these patients.

18 The sponsor did a good job in trying to
19 sort it out but I think we're still left at the end of
20 the day without really knowing what to do with
21 concomitant medications.

22 CHAIRPERSON BECKER: Next we move on to

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1 questions of safety and efficacy. The FDA
2 regulations, specifically 21 CFR 860.7(d)(1) states
3 that there must be a reasonable assurance that a
4 device is safe when it can be determined that the
5 probable benefits to health from use of the device for
6 its intended uses when accompanied by adequate
7 instructions for use and warnings against unsafe use
8 outweigh any probable risks.

9 And so the question for the panel is do
10 the clinical data in the PMA provide reasonable
11 assurance that the device is safe?

12 I'll start with Mr. Balo.

13 MR. BALO: I'm not a medical doctor.
14 Basically I'm an industry representative. You know in
15 dealing with these studies and putting these studies
16 together, industry basically works closely with the
17 physicians, with the medical community, and with the
18 FDA to put forward a study that they feel will be safe
19 and will be efficacious.

20 I think the sponsor -- and to my opinion,
21 from the data they showed, I believe there's a lot of
22 points that are made by Dr. Jensen, by Dr. Fochtman,

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1 if I said your name correctly, about the safety of the
2 device. There are some concerns with young patients
3 and the future effects that the device may have.

4 But looking at and listening to some of
5 the patients speaking today about, I guess, their new
6 lives that they gained back, I would think that from a
7 safety perspective, I think it's a balancing act for
8 me.

9 I would really have to look at the
10 patient. I would look at the condition. But I do
11 think that the data they did show today, at least to
12 me, showed that it was a device that would be safe.

13 CHAIRPERSON BECKER: Ms. Wells?

14 MEMBER WELLS: Again, I think the options
15 are so limited for this particular disease process
16 that we have to consider especially the patients that
17 came forward this morning and spoke to us about their
18 device experiences.

19 So I think this is something that we
20 really need to consider as a panel.

21 CHAIRPERSON BECKER: Dr. Malone?

22 MEMBER MALONE: I would consider safety

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1 against efficacy or, you know, the cost benefit ratio
2 and since I'm not sure that they've shown benefit, I
3 think there are safety concerns. So I think the
4 safety outweighs the benefit.

5 CHAIRPERSON BECKER: Dr. Ortiz?

6 MEMBER ORTIZ: Yes, I believe that the
7 safety is documented by the data presented on the
8 depression studies as well as the seven years with the
9 use in epilepsy.

10 CHAIRPERSON BECKER: Dr. Jensen?

11 DR. JENSEN: I think you've met the burden
12 of saying that this is a safe device when compared to
13 the patients that have epilepsy. I didn't see any
14 increased incidents of problems in this particular
15 group so I don't think the disease process, having the
16 device with this disease process makes a big
17 difference.

18 Again, my big issue is just the 70 percent
19 of patients that have an implantable device that does
20 not work that they now have forever and the long-term
21 implications that go along with that, particularly in
22 further imaging and/or potential surgeries.

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1 Having said that, I still feel that the
2 device is safe but I think the company should
3 certainly look at some way of addressing those
4 patients who have a device that does not show any
5 improvement in their condition. And how, if they so
6 desire, would like it removed, have that done.

7 MEMBER WANG: I have nothing to add beyond
8 what's been said.

9 CHAIRPERSON BECKER: It appears to me that
10 the device is safe. It has some annoying side effects
11 but in general it appears quite safe.

12 MEMBER FOCHTMANN: My impression is also
13 based on the data presented, that the device shows
14 adequate safety, particularly when weighed against the
15 risks of continuing, persistent, treatment-resistant
16 depression.

17 The -- I believe that the registry plan
18 that was outlined earlier would be extremely helpful
19 in providing further information about the long-term
20 effects of the treatment. And I don't know whether
21 it's possible as part of that to also look at specific
22 issues of safety. For example if individuals need

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1 future ECT, safety issues at the time of the ECT with
2 having this device in place, issues along those sorts
3 of lines.

4 So I think that with the evidence that has
5 been presented with the registry follow up plan that I
6 would be comfortable with the safety.

7 MEMBER JAYAM-TROUTH: I agree with Dr.
8 Jensen and I think that maybe, maybe you could
9 evaluate your data a little bit more closely and see
10 why are some people responders and why are some people
11 not responders. Then maybe you don't need to implant
12 it into everybody in the first place.

13 You know you might be able to glean some
14 extra data and see if you need to put it into those 70
15 percent of people who are "non-responders." You know,
16 and as far as the safety in epilepsy now I think it's
17 been established. It's been there for a long time.

18 And there are only a few problems there.
19 But I do not know of long-term studies, you know, on
20 infants. You know I know they have put some of these
21 in infants with Lennox Gastro Syndrome and infantile
22 myoclonic spasms. And these are growing infants. And

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1 I do not know if they have any safety data, you know,
2 on whether this was okay, you know, in those
3 situations.

4 I think that too should be considered
5 because they are among the epilepsy studies.

6 MEMBER ELLENBERG: My sense is that the
7 safety profile has been adequately defined for the age
8 population being considered but the cost benefit ratio
9 issue I agree totally with Dr. Malone. That we don't
10 have, the cost benefit ratio at hand on which to base
11 the safety profile.

12 CHAIRPERSON BECKER: So in summary, Dr.
13 Witten, it sounds like the panel believes that the
14 device is generally safe but based on what is
15 questionable efficacy, it's unclear whether the safety
16 benefit ratio rises to the point that make it
17 something that we should achieve to use.

18 So the final question has to do with
19 efficacy, we're leading right into it then. And this
20 is based on the FDA requirement 21 CFR 860.7(e)(1)
21 which states that there should be a reasonable
22 assurance that a device is effective when it can be

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1 determined, based on valid scientific evidence, that
2 in a significant portion of the target population, the
3 use of the device for its intended uses and conditions
4 of use, when accompanied by adequate directions for
5 use and warnings against unsafe use will produce
6 clinically-significant results.

7 Considering your response to questions 1,
8 2, and 3, do the clinical data in the PMA provide
9 reasonable assurance that the device is effective.

10 So Dr. Ellenberg, would you refresh the
11 microphone?

12 MEMBER ELLENBERG: I don't believe that we
13 have seen adequate evidence of efficacy from the data
14 presented albeit the data has been presented in an
15 excellent way.

16 And I believe that a randomized clinical
17 trial will be the way that we have to see the efficacy
18 determined.

19 MEMBER JAYAM-TROUTH: I agree that it
20 appears that the device is effective.

21 MEMBER FOCHTMANN: I think we have seen
22 some evidence of efficacy. Whether that meets the

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1 rigorous standard required in this question is not
2 totally clear to me. Obviously a more rigorously
3 designed study would help in answering that.

4 CHAIRPERSON BECKER: I think there are
5 certainly hints to efficacy. I think it's not been
6 proved in the way that we're used to seeing other
7 treatments proved in medical trials.

8 MEMBER WANG: I basically think the D-
9 02/D-04 data are essentially not really contributory.

10 But again, I'll just emphasize, I think the acute
11 phase data are extremely positive. In my mind, you
12 know, you had a tendency on the HAM-D and you had a
13 significant finding on the IDS-SR. So I do think
14 there's some evidence, albeit weak for efficacy.

15 But let me just say there's really two
16 questions. One is is it effective? And then second,
17 is it as effective as other modalities such as ECT?

18 And from a public health perspective, that
19 second question is also relevant since you don't want
20 to necessarily divert people from, you know, other
21 potential modalities that might help them.

22 DR. JENSEN: I think I'm struggling with

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1 the same issues as the rest of the panel. It appears
2 to be efficacious in certain patients. And I'm also
3 sensitive to the fact this is a very difficult patient
4 population. Again, I see similar patient populations.

5 Part of me says yes, I'd love to see
6 randomized controlled trials but in my heart I know it
7 would be very difficult to do that with this
8 particular patient populations.

9 I also don't was to see what happened in
10 the Pro Act II Study, which is where we had data of
11 efficacy for intraarterial thrombolysis only to be
12 told we then needed to have another study and the
13 company then decided not to pursue that. And it was
14 never made available to the population.

15 MEMBER ORTIZ: I agree with the comment
16 Dr. Becker made.

17 CHAIRPERSON BECKER: Dr. Malone?

18 MEMBER MALONE: I think in order to show
19 that a treatment is effective in a psychiatric
20 disorder, you need a randomized controlled trial,
21 which is positive. And we don't have one.

22 So I don't think it shows efficacy. I do

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1 think that it is possible to do these studies because
2 you did one. It just was a failed study.

3 CHAIRPERSON BECKER: Ms. Wells?

4 MEMBER WELLS: I agree with Dr. Jensen. I
5 think her remarks are right on.

6 CHAIRPERSON BECKER: Mr. Balo?

7 MR. BALO: I sort of agree with Dr. Jensen
8 and Ms. Wells but I also think, you know, we're sort
9 of looking at this with a drug perspective and when
10 you look at it from a company perspective, they're
11 running this as a device study.

12 And from what I see what the company had
13 did and the long-term effects, there are a group of
14 people that have this disease that could benefit from
15 this device.

16 And, again, balancing that act, I still
17 would say that they have shown that there are patients
18 who could benefit. And this would be effective for
19 those patients.

20 CHAIRPERSON BECKER: So Dr. Witten, it
21 appears we have a little consensus on this question.
22 It seems that some of the panel members believe that

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1 the device has been shown to be effective. Others
2 think more data is needed. And still others think
3 that the device hasn't been shown effective for all
4 patients but at least the hints of efficacy in this
5 very treatment-resistant depression group might signal
6 that it should be okayed for use.

7 So I think with the end of the FDA
8 question, we'll move on to the second open public
9 hearing on the Cyberonics Vagal Nerve Stimulation
10 System, PMA 97003, Supplement 50.

11 Is there anybody from the audience who
12 would like to address the panel now? If so, raise
13 your hand and come toward the podium.

14 (No response.)

15 CHAIRPERSON BECKER: Okay if that's not
16 the case, I think what we'll do is take a ten-minute
17 break. So if everybody could return at 4:25 and we'll
18 vote on the PMA.

19 (Whereupon, the foregoing matter went off
20 the record at 4:16 p.m. and went back on the record at
21 4:30 p.m.)

22 CHAIRPERSON BECKER: It's 4:30, and we'll

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1 get started and try to finish this meeting up.

2 I think that we gave the sponsor a bit of a
3 scare forgetting to mention that we will have
4 summations now, and we'll start with the FDA summation
5 if there is one, Dr. Witten.

6 DR. WITTEN: There is none.

7 CHAIRPERSON BECKER: So we'll move on to
8 Mr. Totah and the sponsor's summation.

9 MR. TOTAH: At this point -- this is Alan
10 Totah, Vice President of Regulatory Affairs -- at this
11 point, I'm going to defer to Dr. Rudolph, but I will
12 join in in a moment. Thank you.

13 DR. RUDOLPH: What we decided to do is
14 we'd like to have several of us address the panel, and
15 I'm going to start. Mr. Totah's going to contribute.

16 Dr. Rush and Dr. Sackheim are both going to
17 contribute as well.

18 The VNS safety data that we presented
19 today, I think the panel agreed with us that although
20 there may be some specific safety issues in genera,
21 the safety is well established, both in the depression
22 trials and in actual clinical use for epilepsy. Side

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1 effects do occur, they're generally mild, stimulation
2 related, tend to diminish over time and rarely cause
3 the patient to discontinue. We didn't find any
4 indication for any specific safety concerns for this
5 specific indication.

6 We'd like Dr. Sackheim to sort of make --
7 we have several topics we want to address, and we're
8 going to ask Dr. Sackheim to talk about clinical
9 benefit in this very ill patient population.

10 DR. SACKHEIM: Yes, thank you, and I
11 understand that this is an important and difficult
12 issue for many of us.

13 When we think about the niceties of
14 research and the purity of designs, we also have to
15 think about the population in which they're going to
16 be applied. One of the things that I think certainly
17 deserves emphasis here is that the types of
18 individuals that are being considered for this
19 treatment are individuals in whom the likelihood of a
20 placebo response, even the consideration of a placebo
21 response are quite small. These are not children,
22 these are not individuals who haven't had many, many

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1 opportunities to demonstrate placebo responses before.

2 What reminds me in the less severe
3 population in our work with electric convulsive
4 therapy at Columbia we have forms of ECT where we have
5 17 percent of the patients responding after full
6 course, depending on where in the brain we stimulate
7 and with what type of electricity. That's acute, and
8 what that means is that there's very little in the way
9 of placebo response in this severe population. That's
10 been demonstrated in studies of oncolytic patients and
11 the psychotically depressed patients.

12 But what's really unusual and what really
13 actually stirred me in looking at the findings with
14 VNS, because for a long time I've been quite critical,
15 was the identification of the long-term benefit in
16 these people, that I simply don't know in any
17 treatment that we can point to that has as much
18 promise in terms of sustaining a benefit if you get
19 there. It's not that a lot of people get there, but
20 if they get there, it looks like they hold and they
21 hold it for a long time.

22 I spent a career working with patients

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1 with treatment-resistant depression. I worked clearly
2 in the area of ECT where our expectations now are that
3 in treatment-resistant patients if we get them better,
4 if they remit, that they become virtually
5 asymptomatic. Seventy percent of patients will lose
6 that benefit within six months. That's pretty much
7 the standard view. This is a context where we have a
8 treatment where it looks like 70 percent will maintain
9 it maybe for two years.

10 So I think there is tremendous promise
11 here, and what we're debating hinges on the importance
12 of one word: randomization. I'm the first to say
13 that hard core clinical work is certainly to be
14 valued, but I also think as you think through this
15 little bit that control over concomitant treatments,
16 the strength of inference in the randomized design in
17 some way become comprised and lack feasibility in this
18 population.

19 And I say that for the following reasons,
20 I'll just give you one quick vignette. Where do you
21 go with standards of care with these patients who have
22 had 20 years in some cases of being in the same

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1 episode in Hamilton at 40 and have been treated by
2 some of the best people in the country? Where we've
3 gone has been to placed in pharmacology that put these
4 people at risk, that's really on the outside of
5 pharmacology, because they're hanging on by a threat.

6 So standard of care is often very dangerous,
7 unacceptable in many ways but have to become
8 acceptable to these individuals.

9 We are going to have a lot of problems
10 with concomitant medications, because you can't keep
11 people for a long-term study in a narrow bind,
12 particularly with these disorders. I would submit
13 that randomization also is going to be a problem
14 because of the selection bias that that would involve.

15 It's that we are offering the same of nothing versus
16 being randomized to something that might be helpful.
17 There may be many patients who would reject that type
18 of compromise and would go then on study.

19 In any case, to summate, the benefit we've
20 seen so far is something that I haven't seen with any
21 intervention for treatment-resistant depression. It's
22 quite unusual. And it echoes, of course, what has

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1 been suggested for epilepsy. I think that very
2 benefit and its nature indicates an effect that can't
3 be accounted for by a fluke of randomization, a fluke
4 of the assignments to different studies and is very,
5 very unusual in the context of treatment-resistant
6 depression. Thank you.

7 DR. RUDOLPH: I want to pick up the
8 randomization theme a little bit, because what I
9 picked up in listening to the panel deliberate is that
10 was the most troubling aspect of the program that we
11 presented to you today.

12 So, first, I would like to talk a little
13 bit about the D-04 as a control. It was obviously a
14 non-randomized control, but it should be thought of
15 as, I think, something more than just a haphazard
16 control. It had many of the elements that would give
17 you a high degree of confidence in its ability to
18 determine effectiveness. It did come from a
19 prospectively designed study, there were overlapping
20 sites, same exact principle enrollment criteria, and
21 it was conducted over a similar time period. So this
22 by itself should have ensured a lot of comparability.

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1 And in fact, as I showed you from the data, it did.

2 And in terms of considering, okay, if
3 that's not good enough, you want a randomized trial,
4 we did talk a lot today about what alternative trial
5 designs might be, and I think for the most part the
6 panel understood the limitations of many of the
7 possibilities, particularly an extended placebo
8 control trial wouldn't be viable in this population.
9 An active treatment control with a single therapy
10 wouldn't work in a population that's already churned
11 through so many different treatments. And, again, if
12 I understood the panel deliberations correctly, I
13 think what most people gravitated to was essentially
14 the D-02, D-04 comparison that we did but do it in a
15 randomized control fashion.

16 I'd ask you to consider a few things.
17 Even randomized control trials, while they are our
18 gold standard, they do not necessarily guarantee that
19 these baseline covariates are equally distributed
20 between groups. And the other issue that was raised
21 was the concomitant medication issue, but even in your
22 deliberations, the way I understood them, you still

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1 came back to allowing the possibility of pretty much
2 access to a variety of medications, as we did in D-04.

3 So, ultimately, what I took away from the
4 discussion was that you would prefer a randomized
5 trial, and the one thing that would do that the D-04,
6 D-02 comparison did not do was it would provide a
7 higher level of confidence that the patient
8 populations did not differ in any significant way. So
9 I think, ultimately, what we're asking the panel to
10 consider is, is that by itself or the greater
11 confidence that you would gain from a randomized
12 control trial, is that by itself enough to delay
13 approval of this therapy; that is, would you gain that
14 much more confidence from randomization which
15 essentially wouldn't address the medication issue any
16 better than the paradigm we used, it would only
17 perhaps, in theory, give you some greater level of
18 confidence that baseline covariates were equally
19 distributed.

20 And as you're considering that question,
21 consider some of the analyses that you saw during the
22 day, particularly, I would say, not only those that

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1 show that the patient groups were very well matched
2 and that the propensity adjustment added some further
3 confidence that the patient groups or that baseline
4 covariates were not the explanation for the
5 difference, but also consider some of the analyses
6 that you may have forgotten about that Dr. Davis
7 presented where we did look at what would be the
8 effect of a single covariate, and we used all the
9 covariates that did differ significantly, the measured
10 covariates, and we used those as examples of if you
11 adjust for that, what is the impact on the effect
12 size, the linear effect, that is, or the p-value and
13 confidence limit. And you saw that any one of those
14 didn't contribute in any meaningful way to the overall
15 statistical significance of the study.

16 So, again, I guess to kind of shorten it,
17 the bottom line would be I would ask you to consider
18 would randomization, which would essentially, if I
19 understand correctly, mainly benefit only in terms of
20 giving some greater theoretical confidence that the
21 patient groups would be comparable than we've already
22 shown, is that worth delaying approval of this product

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1 for?

2 One other issue before we have Dr. Rush
3 close, that we weren't sure that the panel,
4 particularly the people with more of the psychopharm
5 background fully appreciated was the standards for
6 approval of a device, so Mr. Totah will address that,
7 and then Dr. Rush will close.

8 MR. TOTAH: Thank you, Richard. Again,
9 I'm Alan Totah, Vice President of Regulatory Affairs.

10 When the FDA quoted 21 CFR Part 860.70, which has to
11 do with scientific evidence, and charged the panel
12 with the questions that you went through today, what
13 they didn't give you is the full context of that
14 regulation, and I'm going to read to you because we
15 had a question from Dr. Malone that didn't get
16 answered. I tried to get up here but we ran long, and
17 so now's my chance to answer his question.

18 I'll quote out of 21 CFR 860.70. device
19 regulations. "Balanced scientific evidence is
20 evidence from well-controlled investigations,
21 partially controlled studies, studies and objective
22 trials without matched controls, well-documented case

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1 histories conducted by qualified expert and reports of
2 significant human experience with a marketed device."

3 Now, I think important to keep in mind
4 after hearing that regulation for those of you that
5 come from the drug side or pharma side but you may not
6 be familiar with this part of the regulation is keep
7 that mind. Active controls obviously fall within the
8 scope of this regulation.

9 Now, what else I want to tell you is in my
10 earlier speech but just a few more details: History
11 of approved PMAs on the medical device side. Fifty-
12 five percent of all approved PMAs were supported by
13 non-randomized clinical trials. This is for all time.

14 Forty-eight percent do not include randomized control
15 trials. Patients as their own control, or non-
16 randomized active control, fall into that group.
17 Seven percent include no controls whatsoever, and 45
18 percent -- only 45 percent -- include randomized
19 control trials.

20 Now, the basis for what I'm giving you is
21 a CDRH Staff College report on least burdensome
22 provisions of the FDA Modernization Act of 1997, and

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1 I'm giving you information from a March 19, 2000
2 presentation by the CDRH Staff College. I think you
3 need to keep that in mind, or at least I respectfully
4 request that you do that, because that is the
5 difference, one of the differences between the drug
6 side and the device side. Thank you.

7 DR. RUSH: Just briefly, I want to add a
8 brief comment to the issue of efficacy. There are
9 some things in medicine when you see them are
10 pathognomic. You don't see them often but when you
11 see them, it really means a lot, like they really have
12 the illness. So what is pathognomic here about
13 efficacy? I'll just put three on the table.

14 One is the induction of bipolar disorder
15 in 22 percent of patients. We see that in effective
16 antidepressants. I know it's uncontrolled. You have
17 patients who have lost the battery, a battery
18 shutdown, their depression came back. The battery was
19 replaced, the depression went away. That's
20 pathognomic of activity.

21 And, thirdly, you have a predictable
22 course of treatment-resistant depression, unlike other

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1 kinds of depression. The follow-up from the ECT
2 patients, the non-responders to ECT that I showed you
3 in the graph from Dr. Sackheim, continue to be in a
4 terrible state, no better for a year. For the D-04,
5 unchanged as a group for a year. From the Texas
6 Medication Algorithm Project, single-digit sustained
7 response rates, 14 percent, in the best case with
8 algorithm done twice as well in using that as a
9 benchmark, and they're not TRD.

10 So if you have an improvement that grows
11 over time, which appears to be true, looking at it in
12 an uncontrolled fashion with D-02 long term that's
13 pathognomic of activity of the course of illness, is
14 either the same or worsening.

15 Finally, I just want to point out, and I'm
16 sure you are aware because of the patients' testimony
17 and your own knowledge, that this treatment-resistant
18 depression for which we have no other available
19 effective treatments at the moment, is highly lethal
20 and during the time it will take to do another
21 randomized control trial, we'll lose another 1,000 a
22 patients a month, 36,000 if it takes three years.

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1 There's a desperate need out there for this treatment,
2 and I understand that if you look at it and you look
3 at the pathognomic evidence of efficacy as well as the
4 randomized trial evidence, that I think you would
5 persuaded to -- safety having been established -- to
6 approve this device at this time. Thank you.

7 CHAIRPERSON BECKER: Thank you. Ms.
8 Scudiero will now three possible panel recommendation
9 options for pre-market approval applications.

10 DR. MALONE: The biggest threat of
11 regulation that has all these different standards of
12 evidence or something, I can't imagine that you can
13 just pick whichever one you want but that you would be
14 trying to pick the level of evidence that was
15 appropriate to the device; is that right?

16 CHAIRPERSON BECKER: I'll ask Dr. Witten
17 to comment on that.

18 DR. WITTEN: Yes. That's what I was going
19 to say. Those all are acceptable forms of evidence
20 for us, all the ones that he listed. And then for
21 each specific case, as in this case, we're asking the
22 panel to evaluate whether based on what they provided,

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1 whether reasonable assurance of safety and
2 effectiveness has been provided. But that means that
3 everything could be accepted if it provides reasonable
4 assurance of safety and effectiveness.

5 DR. MALONE: But each sort of device could
6 demand a different level; is that true?

7 DR. WITTEN: Yes. I mean, in part, that's
8 part of why we're here is we're asking for your
9 recommendations on this data set for this device.

10 CHAIRPERSON BECKER: Ms. Scudiero?

11 MS. SCUDIERO: Okay. These are on the
12 back of the meeting handouts, the fourth page. The
13 medical device amendments to the Federal Food, Drug
14 and Cosmetic Act, as defined by the Safe Medical
15 Devices Act of 1990, allows the Food and Drug
16 Administration to obtain a recommendation from an
17 expert advisory panel on designated medical device
18 pre-market approval applications, PMAs, that are filed
19 with the agency. The PMA must stand on its own
20 merits, and your recommendation must be supported by
21 the safety and effectiveness data in the application
22 or by the applicable publicly available information.

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1 Safety is defined in the Act as reasonable
2 assurance based on valid scientific evidence that the
3 probable benefits to health under the conditions of
4 intended use outweigh any probable risks.
5 Effectiveness is defined as reasonable assurance that
6 in a significant portion of the population the use of
7 the device for its intended uses and conditions of use
8 when labeled will provide clinically significant
9 results.

10 Your recommendation for the vote are as
11 follows: One, approvable if there are no conditions
12 attached; two, approvable with conditions. The panel
13 may recommend that the PMA be found approvable subject
14 to specified conditions such as physician or patient
15 labeling education, labeling changes or further
16 analysis of existing data. Prior to voting, all the
17 conditions of approval should be discussed by the
18 panel. Three, not approvable. The panel might
19 recommend that the PMA is not approvable if the data
20 do not provide reasonable assurance that the device is
21 safe or if a reasonable assurance has not been given
22 that the device is effective under the conditions of

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1 use prescribed, recommended or suggested in the
2 proposed labeling.

3 Following the voting, the Chair will ask
4 each panel member to present a brief statement
5 outlining the reason for his or her vote.

6 CHAIRPERSON BECKER: Is there a motion
7 from the panel? Dr. Wang?

8 DR. WANG: Approvable with conditions.

9 CHAIRPERSON BECKER: Is there a second for
10 the motion?

11 PARTICIPANT: Second.

12 CHAIRPERSON BECKER: I hear a second. So
13 at this point, I guess I will entertain an amendment
14 to the main motion for the first condition of
15 approvability. Is there a motion for a condition of
16 approvability?

17 DR. WANG: Yes. The condition, I wonder
18 if it wouldn't be helpful to have a condition for both
19 scientific and also public health reasons that there
20 be a failure of more than two or more trials, to maybe
21 something like four or five, and here's my reasoning.
22 The scientific reason is I think we may be going

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1 beyond the generalized ability of the data. You
2 showed us data suggesting that these people have --
3 they had nearly four, on average, fail trials just in
4 this episode, and on average I think it was 12 or so
5 failed trials. So to extend these results to a
6 population that may have only failed two trials may be
7 going beyond the limits of this data.

8 The second is a public health reason, and
9 that is given the, let's say, less than robust data
10 right now on efficacy, I think there's a concern,
11 public health concern, which I alluded to earlier,
12 that patients who have only failed two trials, and you
13 can get there pretty fast, you just have to fail two
14 medication trials in the span of a few weeks and you'd
15 be eligible for this, you might forego modalities
16 which have a much stronger evidence for them. And by
17 that I mean ECT, lithium augmentation, maybe dual
18 modalities, psychotherapy, plus medications that
19 haven't been tried.

20 So I think if you raise the bar to four or
21 more failed trials or five or more failed trials,
22 something like that, you at least would ensure that

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1 patients have had a chance to go through some of the
2 modalities that have stronger evidence bases than I
3 think currently exist for VNS.

4 CHAIRPERSON BECKER: So, Dr. Wang, would I
5 be correct in saying that your motion would be that
6 patients need to fail at least four trials of approved
7 medical therapy?

8 DR. WANG: I would take guidance here from
9 sort of the other -- the clinicians in the room how
10 many sort of modalities do we think have at least as
11 much evidence suggesting their efficacy. My guess is
12 four or five, something like that.

13 CHAIRPERSON BECKER: Is there anybody who
14 seconds that motion?

15 DR. FOCHTMANN: I would second that
16 motion.

17 CHAIRPERSON BECKER: Do you want to add on
18 a little bit?

19 DR. JAYAM-TROUTH: Can I kind of add on a
20 little bit.

21 CHAIRPERSON BECKER: Sure.

22 DR. JAYAM-TROUTH: Thank you. I think at

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1 this point that indication statement where you have
2 indicated in your write-up that VNS therapy indicated
3 for use as an adjunctive long-term treatment of
4 chronic or recurrent depression for patients over the
5 age of 18 who are experiencing a major depressive
6 episode but has not had an adequate response to two or
7 more adequate antidepressant treatments needs to be
8 definitely modified. I agree with Dr. Wang, and I
9 also think that it should be for treatment-resistant
10 depression that should be considered.

11 CHAIRPERSON BECKER: Would anybody like to
12 discuss this motion for approval -- this condition of
13 approval, I mean? No further comments? So if that's
14 the case, then I guess we're ready to vote on the
15 first condition of approval. We'll do each one
16 individually, so we'll go on the first one.

17 All in favor of the first condition of
18 approval, which is that patients must fail at least
19 four or more trials or somewhere thereabouts of
20 medical therapy prior to implantation with a VNS,
21 please raise their hand.

22 So Dr. Jayam-Trouth, Dr. Fochtman, Dr.

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1 Jensen, Dr. Wang, so that's four.

2 All opposed to the first condition of
3 approval, please raise your hands. Dr. Ortiz.

4 And all abstaining from voting on this
5 condition of approval. Dr. Ellenberg and Dr. Malone.

6 DR. MALONE: I wouldn't vote for approval,
7 so I don't know how to vote on this condition.

8 CHAIRPERSON BECKER: So you're abstaining
9 then.

10 Does anybody have a second condition that
11 they would like to move for approval?

12 DR. JENSEN: I have a couple, actually.
13 The first has to do with MD education once the device
14 is approved and anybody can use it, and it's not going
15 to be in the 20 centers where the best of the best are
16 doing procedures. So I think we have to look at the
17 lowest common denominator. I think surgeons should be
18 identified by the number of nectosections they do a
19 year, and there should be a minimum number of
20 nectosections they do a year to show that they are
21 actually capable of implanting the device.

22 I think there needs to be identification

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1 of the psychiatrists and their ability to show
2 appropriate use of the device in patients, not just in
3 the lab and --

4 CHAIRPERSON BECKER: We need to go one by
5 one.

6 DR. JENSEN: One by one. Okay.

7 CHAIRPERSON BECKER: Does anybody -- would
8 anybody like to second Dr. Jensen's condition 2 that
9 the surgeons need to be identified for the number of
10 nectosections they do and their ability to perform
11 those nectosections? A second for that motion?

12 DR. FOCHTMANN: Second.

13 CHAIRPERSON BECKER: So we have a second
14 from Dr. Fochtmann. So at this point, we need to vote
15 on that second condition. All in -- or any discussion
16 before we move on this motion? Anybody want to --

17 DR. JAYAM-TROUTH: Yes. I have a point,
18 and that is that many people will be starting new and
19 fresh, and you can't tell them, "How many have you
20 done," when they've none at all. I think there should
21 be teaching for them so that they are familiar with it
22 and they can do it. But then to stipulate that you

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1 have to have ten when they have to start, I think it's
2 not feasible.

3 CHAIRPERSON BECKER: I guess I would say
4 that most vascular surgeons or neurovascular surgeons
5 will have done nectosections, so that shouldn't be an
6 issue. Putting the leads on may be new for them and
7 that's probably not as big a concern, but I think the
8 surgeons should at least know how to get into the neck
9 safely, into the carotid sheath safely.

10 All right. So let's take a vote for the
11 second condition of approval, which is that the
12 surgeons need to be identified for their ability to
13 operate in the carotid sheath.

14 All in favor of the second condition of
15 approval raise your hands. And that would be Dr.
16 Ortiz, Dr. Jensen, Dr. Wang, Dr. Fochtman and Dr.
17 Jayam-Trouth.

18 All against this condition of approval?
19 All opposed?

20 And all abstaining? That would be Dr.
21 Malone -- and Dr. Ellenberg, sorry.

22 Any motions for a third condition for

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1 approval? Dr. Jensen?

2 DR. JENSEN: Again, in terms of MD
3 education, I similarly like to see the psychiatrists
4 identified as their ability to show appropriate use of
5 the device in patients, not just necessarily in the
6 lab, but they should be required to take a course and
7 then have their first three, four patients checked in
8 some manner to make sure the programming is
9 appropriate.

10 CHAIRPERSON BECKER: So Dr. Jensen would
11 like psychiatric training for programming the VNS
12 device. Anybody second that motion?

13 DR. JAYAM-TROUTH: Second.

14 CHAIRPERSON BECKER: Dr. Jayam-Trouth. So
15 anybody like to discuss that point that psychiatric
16 education should be included in the condition for
17 approval?

18 DR. ORTIZ: I wonder if it should be
19 expanded, because it's not necessarily just
20 psychiatrists who might program that. I mean we may
21 be talking about behavioral neurologists or other
22 people, so it's more of an engineering kind of thing.

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1 CHAIRPERSON BECKER: So essentially any of
2 the clinicians who will be taking care of these
3 patients and need to have training prior to being able
4 to have a patient implanted.

5 DR. FOCHTMANN: Would this be -- would you
6 perceive this as requiring as some sort of specific
7 certification or just showing that you've gone to a
8 continuing education course?

9 DR. JENSEN: Well, I think that, clearly,
10 you have to go to a course that should be run by the
11 company on how to use the device, but for me the issue
12 always comes down to when you're doing it in the lab
13 by yourself for the first time, did you do it right?
14 And so I think there needs to be a mechanism to make
15 sure that you've said you've set this thing to a
16 certain standard and that's correct.

17 Now, I don't use the device, maybe it's
18 very simple and all it would take is somebody from the
19 company coming behind and saying, "Check," or somebody
20 else who already uses the device in the hospital
21 checking or whatever, but I just want to make sure
22 that when people are getting an implantable device,

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1 that it's being programmed correctly, and that that's
2 somehow documented.

3 CHAIRPERSON BECKER: Okay. So I think
4 it's time to vote on this condition for approval,
5 which is that the clinicians who are caring for these
6 patients who have devices implantable need to show
7 some sort of documentation that they are able to
8 understand how to program and change the parameters of
9 simulation on the device.

10 All in favor of this motion raise their
11 hands. So Dr. Ortiz, Dr. Jensen, Dr. Wang, Dr.
12 Fochtmann and Dr. Jayam-Trouth.

13 All opposed to this condition for approval
14 raise your hand?

15 And everyone abstaining from this vote.
16 Dr. Ellenberg and Dr. Malone.

17 Are there motions for any other conditions
18 for approval? Dr. Jensen?

19 DR. JENSEN: For patient education, I
20 think that it needs to be clearly stated, and the
21 patients know that the device implant may affect their
22 ability to have diagnostic or therapeutic procedures

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1 in the future and that they do have the option of
2 having the device removed if need be, if they are a
3 non-responder or whatever and they want to have it out
4 and that they receive some sort of identification
5 bracelet, card, et cetera, that identifies them as
6 having this implant and what the implications are for
7 MR use or other sorts of imaging surgeries.

8 CHAIRPERSON BECKER: So it sounds like
9 this condition for approval has to do, in part, with
10 labeling, and, obviously, as part of, I think, any
11 delivery of medical care, we'd want to inform our
12 patients completely of the risks and benefits involved
13 in having the device implanted, which include the
14 risks of having a limited ability to obtain diagnostic
15 radiographic tests, and so that needs to be very
16 clearly spelled out to the patients and perhaps have
17 some sort of identification that they carry with them
18 like someone who has a pacemaker and carry an
19 identification with them.

20 Is there anybody who seconds this motion?

21 DR. JAYAM-TROUTH: Second.

22 CHAIRPERSON BECKER: There's a second. So

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1 everybody in favor of condition 4, which is patient
2 education and some sort of identification for the
3 patients that they have this VNS device implanted,
4 please raise your hands. I'm sorry, before we raise
5 our hands, discussion points, I'm sorry. Seems pretty
6 straightforward. Anybody want to discuss that point?

7 No?

8 All right. So now everybody in favor of
9 Condition 4 raise your hands. Again, it seems like
10 our usual group: Dr. Jensen, Dr. Wang, Dr. Fochtman
11 and Dr. Jayam-Trough and Dr. Ortiz. Did I see your
12 hand there or not?

13 DR. ORTIZ: Yes, you saw it.

14 CHAIRPERSON BECKER: Okay. All opposed to
15 this condition for approval raise your hands.

16 And all abstaining from voting? Dr.
17 Malone and Dr. Ellenberg.

18 Any motions for further conditions for
19 approval? We've exhausted you, Dr. Jensen?

20 DR. JENSEN: Well, I do have one question
21 about the registry. Can we ask that certain data be
22 culled from the registry? They're planning on having

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1 a registry, but one of the things that I would like to
2 see is that the parameters that are looked at in the
3 registry are evaluated for patients who are non-
4 responders looking for particular group types that are
5 non-responders, and if we find one, that this is a
6 group of patients who do not respond to this device,
7 unequivocally, that that could then end up being a
8 contraindication for use.

9 CHAIRPERSON BECKER: So let me ask,
10 actually, Dr. Witten, is that something that we can
11 request that the sponsor do to collect certain data in
12 the post-marketing registry to the FDA?

13 DR. WITTEN: Yes, especially given that
14 Dr. Jensen has stated a specific purpose for this.

15 CHAIRPERSON BECKER: So with that motion
16 for identifying specific clinical data be collected in
17 the patient registry, is there anybody who'd like to
18 second that motion?

19 DR. JAYAM-TROUTH: Second.

20 CHAIRPERSON BECKER: Dr. Jayam-Trouth
21 seconds that motion. And anybody want to discuss this
22 point any further?

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1 DR. FOCHTMANN: I'd like to discuss this.

2 I think that it's a reasonable idea to collect the
3 data. I am a little bit concerned about identifying
4 specific subgroups of individuals who would be then
5 designated as being contraindicated to receive this
6 device, because I think, as has already been quite
7 well described, this is a treatment that people go to
8 when they really don't have other viable options, and
9 I don't think that any statistical analysis that shows
10 that one subgroup was less likely to respond is going
11 to be an absolutist sort of subgroup, and so I would
12 be very concerned on the basis of subsequent analysis
13 thereby denying a potentially effective treatment to
14 individuals in need.

15 DR. JENSEN: Yes. I guess I should have
16 clarified when you asked the question about what FDA
17 is allowed. If we got information that showed that
18 there were certain prognostic factors which gave you a
19 better idea of when a patient would respond, that
20 would typically be used in a labeling update.
21 Typically, contraindications are when there is a
22 safety problem that's been identified with the device.

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1 So I was just responding to the question about
2 whether you could ask for this data in the registry,
3 not about the other part of the recommendation, about
4 contraindication.

5 DR. FOCHTMANN: I would just like that
6 information in the labeling.

7 DR. JENSEN: Right.

8 DR. JAYAM-TROUTH: One other thing: Would
9 it interfere with the HIPAA and all that, the
10 regulations, with the demographic, et cetera, that we
11 collected and put out there in the registry, anybody
12 could get access to it? Wouldn't that come in the way
13 of patient confidentiality?

14 DR. WITTEN: If the Sponsor's planning a
15 registry, then I'm assuming that they've looked at how
16 they were going to do that in such a way that wouldn't
17 be in contradistinction to what they're required to do
18 under HIPAA.

19 DR. FOCHTMANN: Would that same issue of
20 HIPAA also apply to manufacture or checking device
21 parameters and operation, that they would check on
22 that as well? I'm not used to a situation where

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1 manufacturers are watching me or in the room with me
2 when I'm taking care of patients.

3 DR. WITTEN: Let me say, I'm not an expert
4 on HIPAA, but a lot of it would depend on how it was
5 done and what the patient was informed of, I think.
6 But what we're looking for from you, the Panel, is
7 your recommendations about the kinds of -- if you're
8 recommending things in a registry or further
9 information to be collected, we're looking to you for
10 recommendations about the kinds of information you'd
11 be interested in and how you would see this
12 information being used to further public health and
13 not the specifics of exactly how something would get
14 done. That's something we would discuss later if we
15 decided to implement those conditions. That's the
16 kind of thing we would discuss specifics with the
17 sponsor. So I don't think you need to be concerned
18 about those questions. We'd like to hear what it is
19 you think is needed or you'd like to recommend.

20 DR. JAYAM-TROUTH: Can I kind of voice
21 another concern? I don't know if it's a
22 recommendation but my concern is that this is still

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1 only a short time for this device. We're talking
2 about just a few years, and I'm not sure down the road
3 maybe some of the side effects will come. Can we
4 stipulate now that at the moment that if some extra
5 side effects are seen or something else happens, that
6 it's brought to the attention of the FDA or is that
7 normal?

8 DR. WITTEN: There is a process by which
9 sponsors are required to report to us on a periodic
10 basis and report to the MDR system also new safety
11 information about the device. That doesn't need its
12 own condition, unless there's some specific thing
13 you're asking us to look for.

14 CHAIRPERSON BECKER: Dr. Witten, would you
15 like the Panel now to make some recommendations about
16 the data to be collected or is this something that
17 could be worked out after the meeting between the FDA
18 and the Sponsor?

19 DR. WITTEN: Well, so far what I've heard
20 is a registry to try to identify prognostic factors to
21 determine who might best benefit from this device. Is
22 that right?

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1 DR. JENSEN: Correct.

2 DR. WITTEN: Okay. And so if you have any
3 -- it's up to the Panel. The Panel can either stop
4 there or if the Panel has any specific suggestions
5 about the kind of data that they think would be useful
6 to collect in an effort these prognostic factors, that
7 would be useful too. So it depends on whether you
8 want to add anything to that.

9 CHAIRPERSON BECKER: Does anybody on the
10 Panel have any thoughts about what other pieces of
11 information should be collected of what else we should
12 look for in collecting information for the registry?
13 What pieces of information do we want to get out of
14 it, what do we want to learn?

15 DR. FOCHTMANN: I would think, obviously,
16 information about the stimulus settings and not just
17 including pulse widths and the other aspects of the
18 stimulus parameters, information, obviously, about
19 efficacy in terms of patient perceptions and in terms
20 of clinician perceptions, obviously information about
21 safety, adverse effects. Those would be the key
22 elements in addition to the other patient

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1 characteristics, concomitant medications, things like
2 that.

3 CHAIRPERSON BECKER: Any other thoughts or
4 discussion?

5 DR. ORTIZ: I guess I would want to follow
6 what you were suggesting. It seems like, at least
7 from the Pharmacology Committee, that a lot of that is
8 better worked out between the FDA and the Sponsor
9 directly.

10 CHAIRPERSON BECKER: So with that, I think
11 it's the recommendation of the Panel that the pre-
12 market approval application, P970003 -- there's more
13 conditions? I'm sorry. So I think there is a motion
14 for another condition.

15 DR. JENSEN: Well, have you voted on the
16 registry?

17 CHAIRPERSON BECKER: I think we voted on
18 it before we talked about the specific information to
19 be collected.

20 DR. FOCHTMANN: The motions that I had
21 related to specific aspects of the wording on the
22 labeling claim. Is that something that is appropriate

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1 to comment on?

2 CHAIRPERSON BECKER: Sure.

3 DR. FOCHTMANN: The first comment that I
4 would have is that on Points 2, 3 and 4, I think it
5 should specifically state 12-month open label follow-
6 up of the randomized control trial so that it doesn't
7 give the impression that there was a 12-month
8 randomized control trial to the person who is not
9 totally familiar with these studies.

10 CHAIRPERSON BECKER: Is there a second to
11 the motion in changing that labeling information?

12 DR. WANG: Second.

13 CHAIRPERSON BECKER: Dr. Wang seconds it.
14 Any discussion on that point?

15 Everybody in favor of changing the
16 labeling to reflect the fact that it was not a 12-
17 month randomized control trial raise their hands. Dr.
18 Ortiz, Dr. Jensen, Dr. Wang, Dr. Fochtmann and Dr.
19 Jayam-Trouth.

20 Everybody opposed to that motion raise
21 their hands.

22 And everybody abstaining? Drs. Malone and

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1 Ellenberg. Thank you.

2 DR. FOCHTMANN: The second wording issue
3 that I would have would be in Point 4. Since there
4 was a degree of variability in the results of the
5 trials depending on what outcome measure was used, I
6 think that the phrase, "highly statistical significant
7 p less than 0.0001," should be changed to, "showed a
8 significant," and there's a word missing there,
9 "effect for treatment."

10 CHAIRPERSON BECKER: So the motion is to
11 change the wording from, "highly statistically
12 significant effect," to just, "a significant effect."
13 Is there a second for that motion?

14 DR. FOCHTMANN: And to delete the, "p less
15 than 0.0001."

16 CHAIRPERSON BECKER: And delete the p
17 value. A second for that motion?

18 DR. WANG: Second.

19 CHAIRPERSON BECKER: Dr. wang. Any
20 discussion on that motion?

21 Everybody in favor of changing that
22 labeling information raise their hands. Dr. Ortiz,

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1 Dr. Jensen, Dr. Wang. Dr. Fochtmann, Dr. Jayam-Trouth.

2 Everybody opposed?

3 Everybody abstaining? Drs. Malone and
4 Ellenberg.

5 DR. FOCHTMANN: The next wording point
6 that I would have is in Point Number 6 where it says,
7 "VNS therapy should be considered." I would like to
8 suggest that that be changed to, "VNS therapy may be
9 considered," since I don't believe that it's fair to
10 say that any treatment absolutely has to be considered
11 for every patient.

12 DR. JAYAM-TROUTH: Second.

13 CHAIRPERSON BECKER: Second. Thank you.
14 Any discussion on that point?

15 Everybody in favor of changing the
16 labeling to, "VNS therapy may be considered," as
17 opposed to, "should be considered," raise their hands.

18 Dr. Ortiz, Dr. Jensen, Dr. Wang, Dr. Fochtmann, Dr.
19 Jayam-Trouth.

20 Everybody opposed?

21 And everybody abstaining? Drs. Ellenberg
22 and Malone. Thank you.

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1 DR. FOCHTMANN: And my final suggested
2 amendment is Point 12, which states, "Brain imaging
3 studies have demonstrated that VNS modulates blood
4 flow and/or metabolism in many areas of the brain that
5 are affected to mood disorders." I would suggest that
6 the data that's presented, although very interesting,
7 is in small groups of individuals and would be
8 considered, I believe, to be most people to be
9 preliminary data, and I would suggest that this point
10 be deleted entirely.

11 DR. JAYAM-TROUTH: Second.

12 CHAIRPERSON BECKER: Thank you. And is
13 there any discussion on this point?

14 Everybody in favor of deleting information
15 on blood flow changes with VNS stimulation may I see
16 your hands? Dr. Ortiz, Dr. Jensen, Dr. Wang, Dr.
17 Fochtmann and Dr. Jayam-Trouth.

18 Everybody opposed to deletion of this
19 point?

20 And everybody abstaining? Dr. Malone, Dr.
21 Ellenberg.

22 DR. FOCHTMANN: Actually, I do have one

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1 more.

2 (Laughter.)

3 And this just parallels the change that
4 was made in the proposed indication. Point Number 6
5 continues to read, "two or more antidepressant
6 therapies." I would change this to read, "VNS therapy
7 should be considered for patients with chronic or
8 recurrent depression who have received an inadequate
9 response to treatment or who have experienced
10 intolerable side effects to four or more
11 antidepressive therapies."

12 CHAIRPERSON BECKER: Is there a second for
13 that change in the labeling?

14 DR. JENSEN: Second.

15 CHAIRPERSON BECKER: Dr. Jensen. Any
16 discussion on this point?

17 Everybody in favor of changing the
18 labeling to reflect the fact that a patient needs to
19 be intolerant of or have failed at least four adequate
20 treatments for depression please raise their hands.

21 Dr. Jensen, Dr. Wang -- are your hands
22 down? Dr. Jensen and Dr. Jayam-Trouth. So that's

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1 two.

2 Everybody opposed to this change in
3 labeling?

4 And everybody abstaining from voting on
5 this point?

6 DR. FOCHTMANN: Could I just ask for a
7 clarification why you're abstaining since this would
8 presumably make it parallel with the change you made
9 before?

10 DR. WANG: You have the tightening up sort
11 of the restriction that you have to fail trials, I
12 think, is based on sort of the efficacy. I primarily
13 thought that would be useful based on the sort of
14 limited evidence base of the efficacy. When you start
15 mixing in potential intolerance, I have to think it
16 through, but I wonder if it doesn't -- you might not
17 get, sort of, folks going into the treatment having
18 bypassed, again, treatments that may have a stronger
19 evidence base behind them, and I mean evidence base
20 for efficacy, not safety. So it undermines -- it
21 potentially undermines that kind of filter I'm
22 suggesting or wanted to suggest to kind of ensure that

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1 patients have tried multiple, sort of more solidly
2 supported treatments on the efficacy side.

3 DR. JAYAM-TROUTH: That's one of the
4 reasons I said we should use the word, "treatment-
5 resistant depression."

6 CHAIRPERSON BECKER: So I just want to
7 clarify this point for myself. Your suggested changes
8 for this point are what again?

9 DR. JAYAM-TROUTH: That we use the word
10 not just "chronic depression" or "multiple episodes of
11 depression" but use "treatment-resistant depression."

12 CHAIRPERSON BECKER: And, Dr. Fochtmann,
13 you wanted the exact wording?

14 DR. FOCHTMANN: I was just trying to
15 change the wording of Point 6 to incorporate the
16 change that Dr. Wang had made to the proposed
17 indication. Based on what he said in response to my
18 question about why he abstained, I mean I think to
19 have two or more in Point 6 and four or more in Point
20 1 is discordant. To say four or more here and
21 delete the information about intolerable side effects
22 might be an alternative way to do it.

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1 DR. ORTIZ: And I might just add that my
2 objection is that I'm not clear that a failure of four
3 antidepressants is the established standard for
4 treatment-resistant depression.

5 DR. WANG: Let me just say, I'm not -- the
6 goal in sort of proposing that wasn't to define a
7 population of treatment resistance, it was to ensure
8 that patients have gone -- who have treatment-
9 resistant depression, whatever the definition, I'll
10 just assume that we have a correct definition, have
11 had the opportunity to try other treatments that have
12 a little bit more support for them than currently VNS
13 seems to have.

14 DR. ORTIZ: Which includes ECT. So I
15 guess that's my concern, it's too narrow.

16 DR. WANG: Maybe I'm misunderstanding your
17 --

18 DR. ORTIZ: Yes, that the four is pretty
19 limiting as far as the definition of that, that the
20 population that's been used is ECT or two failures or
21 -- I mean ECT has been an option as well.

22 DR. JAYAM-TROUTH: Does anyone know the

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1 DSM-4 definition of treatment-resistant depression?

2 DR. FOCHTMANN: I don't believe that's
3 DSM-4 category.

4 CHAIRPERSON BECKER: So it sounds like
5 we're at a sticky point here, because that goes back
6 to your initial point now.

7 DR. WANG: Yes. Again, let me just
8 reiterate. The goal is not to, sort of, create a
9 definition of what treatment resistance is. It's
10 more, sort of, from the practical point of view of
11 just ensuring that whatever the person has, I'm
12 assuming it's treatment-resistant depression, have had
13 adequate trials of enough therapies that we then --
14 that they're then potentially eligible for a treatment
15 that has marginal efficacy data to it. I mean that's
16 --

17 DR. FOCHTMANN: I certainly agree with
18 that, but, again, my feeling is that the FDA has
19 historically worked those things out with the sponsor
20 very well.

21 DR. WANG: Yes. I leave the exact number
22 up to FDA, whatever. It's questionable what should

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1 maybe have come first in terms of having a stronger
2 evidence base and what may come after that's
3 completely unsupported. That's something maybe to
4 sort of think about and work out. But Dr. Fochtmann's
5 --

6 DR. FOCHTMANN: Yes. My main point is
7 just that the change that I thought we made in Point 1
8 needs to be consistent in Point 6.

9 DR. WANG: Yes. And I agree, and your,
10 sort of, last suggestion I think I did agree with it,
11 if I understood it correctly, which was to drop the --

12 DR. FOCHTMANN: Intolerance?

13 DR. WANG: Yes, drop the intolerant
14 passage.

15 DR. FOCHTMANN: So do I need to restate
16 the modified --

17 CHAIRPERSON BECKER: Please do.

18 DR. FOCHTMANN: -- condition. So the
19 modified condition would be, "VNS therapy should be
20 considered for patients with chronic or recurrent
21 depression who have experienced an inadequate response
22 to treatment with four or more antidepressant

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1 therapies, period."

2 DR. JAYAM-TROUTH: May be considered.

3 DR. FOCHTMANN: May be considered. Yes,
4 you're correct. Thank you.

5 CHAIRPERSON BECKER: So can we take a vote
6 on that modification?

7 All in favor of that modification, as
8 read, please raise your hands? Dr. Jensen, Dr. Wang,
9 Dr. Jayam-Trouth and Dr. Fochtmann.

10 All opposed to that modification? Dr.
11 Ortiz.

12 And people abstaining? Dr. Malone and Dr.
13 Ellenberg.

14 Is there a motion for any more conditions?
15 Dr. Ellenberg?

16 DR. ELLENBERG: I would like to move that
17 as a condition of approval there be conducted a Phase
18 IV trial for efficacy to better define the cost-
19 benefit ratio -- excuse me, a randomized control
20 clinical trial.

21 CHAIRPERSON BECKER: So the motion is for
22 conduct of a Phase IV randomized controlled trial to

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1 better show efficacy. Is there a second for that
2 motion? So the motion is seconded by Drs. Wang and
3 Malone. And I need to just a question because doesn't
4 that actually suggest that you don't want to approve
5 this, that you want to go back into another trial?

6 DR. WANG: Did you say Phase IV?

7 DR. ELLENBERG: Not at all. This is if
8 the drug is approved, then using a Phase IV to refine
9 what needs to be used by physicians prescribing this
10 procedure of VNS. It doesn't preclude the use of the
11 drug under the approval.

12 CHAIRPERSON BECKER: Dr. Witten, you have
13 a comment?

14 DR. WITTEN: Well, just a little
15 clarification so people know what they're voting on,
16 so that's what I'll say, is just that if you vote to
17 approve the device as a group, as a Panel, you're
18 telling us that you think a reasonable assurance of
19 safety and effectiveness has been demonstrated
20 already. So if you are recommending that with this
21 specific condition, then we would -- I guess we would
22 look at as specifically refining what's already known

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1 about the product. I just would like to understand
2 the condition, because if you recommend approval,
3 you're recommending that reasonable assurance of
4 safety and effectiveness has already been
5 demonstrated. So what specifically will we be looking
6 for in this study?

7 DR. ELLENBERG: Primarily, a rigorous
8 estimate of the efficacy of VNS that can be used in
9 prescribing VNS and that could be weighed against
10 additional safety data as well as the historical data
11 already available.

12 DR. FOCHTMANN: Just as a point of
13 information, where it says the information about
14 approvable with conditions, it says a number of
15 things, including labeling changes, physician and
16 patient education or further analysis of existing
17 data. Is a request for an additional trial allowable
18 as part of this particular vote that is currently on
19 the floor?

20 DR. WITTEN: You can make any
21 recommendation if it's to answer a specific question.
22 So if it's to answer a question, then it's something

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1 that could be conceivably part of a post-approval,
2 recommendation of post-approval study. If it's to
3 provide a reasonable assurance of safety and
4 effectiveness, then it wouldn't be a post-approval.
5 But as Dr. Ellenberg phrased it, to refine their
6 estimate or refine -- provide a more rigorous estimate
7 of effectiveness, I guess you could consider that a
8 focused question.

9 DR. WANG: And I think in addition to,
10 sort of, greater precision and maybe more --
11 potentially more valid data, there's also this issue
12 of subgroups. We have no idea does this work in
13 patients with bipolar major depressive episodes, and
14 these sorts of questions really would require, I
15 think, sort of additional data to help sort of sort
16 out who is this treatment potentially good for or best
17 for.

18 CHAIRPERSON BECKER: So can we take a vote
19 on this condition of asking the Sponsor to perform a
20 --

21 DR. ELLENBERG: You need a second.

22 CHAIRPERSON BECKER: It was seconded down

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1 here.

2 DR. ELLENBERG: Okay. Sorry.

3 CHAIRPERSON BECKER: Yes. So a vote on
4 the suggestion that we have the Sponsor perform a
5 Phase IV study to better refine the estimates of
6 efficacy of this device.

7 All in favor of this condition, please
8 raise their hands. Dr. Malone, Dr. Wang, Dr.
9 Fochtman and Dr. Ellenberg.

10 All opposed to this condition raise their
11 hands.

12 All abstaining?

13 Actually, everybody who is in favor of the
14 condition please raise your hand again. Okay.

15 Everybody opposed? Okay. There we go.

16 And everybody abstaining?

17 All right. Any further motions for
18 conditions?

19 DR. JAYAM-TROUTH: Actually, I didn't
20 understand that properly myself, the last one.

21 CHAIRPERSON BECKER: Yes. I actually have
22 conditions myself, and it seems to me kind of that

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1 we're asking them to do a whole other study which then
2 means they shouldn't be approved.

3 DR. JENSEN: I think some of the data that
4 you may be looking for could be obtained through the
5 registry. I realize it's not a randomized controlled
6 trial, but if what you're looking for is targeting
7 specific groups or treatment types that may or may not
8 show efficacy with this device, you'll get some
9 information from the registry. I realize it's not
10 rigorous science.

11 CHAIRPERSON BECKER: So I hate to belabor
12 this point, but --

13 DR. JAYAM-TROUTH: I have one other
14 question. Is there anything like a Phase IV for a
15 device?

16 DR. WITTEN: Well, we certainly have a
17 variety of ways of collecting information post-
18 approval or asking the sponsor -- more accurately
19 asking the sponsor to collect information post-
20 approval, and these range from additional bench
21 testing to registries. And we've also had sponsors
22 continue to follow patients in studies that they've

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1 already enrolled patients in. But we also have had
2 new perspective studies in the post-approval phase to
3 answer specific focused questions, not to demonstrate
4 that the device is safe and effective, but to answer
5 specific focused questions about the product. So this
6 wouldn't be -- that part of it we've done before. We
7 have other studies that have done that.

8 CHAIRPERSON BECKER: I suspect it would be
9 very difficult to get a patient who's got chronic-
10 resistant depression to agree to be in a randomized
11 controlled trial once the device is approved. I just
12 don't think it's going to happen. So I wonder how we
13 could actually do this study if the device is
14 approved. Somebody have any thoughts about that?

15 DR. MALONE: Patients enroll in Phase IV
16 trials that are controlled all the time. I mean we in
17 doing child psychiatry we're always doing post-
18 approval studies, and they could get the drug
19 anywhere, but they still enroll in the studies.

20 DR. JAYAM-TROUTH: Yes, but that's a drug.
21 This is a device.

22 DR. MALONE: But I don't know why they'd

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1 -- I think you could recruit for a study like that.

2 CHAIRPERSON BECKER: Dr. Wang?

3 DR. WANG: Yes. Plus you could do it for
4 the short term, and you also -- you have to remember
5 this is adjunctive treatment. The patients could get
6 standard of care so they're not on nothing. So I
7 think ethical issues might -- there doesn't appear to
8 be as many ethical issues, and I think there might not
9 be as much patient resistance.

10 DR. FOCHTMANN: The other issue is that
11 there are fairly clear benefits for many individuals
12 of being able to be followed closely for management of
13 their illness in a systematic fashion that they don't
14 gain by care as usual in the community. And so for
15 the reasons, some people are willing to enroll in such
16 trials.

17 DR. MALONE: The other thing is I don't
18 know if insurance is going to pay for this, so it
19 would be a way to get free treatment for some
20 individuals.

21 CHAIRPERSON BECKER: Dr. Ellenberg, would
22 you envision this trial to be a short-term or long-

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1 term trial?

2 DR. ELLENBERG: I would leave that up to
3 FDA. My impression is from the evidence presented
4 today that one year would be appropriate.

5 CHAIRPERSON BECKER: Motions for other
6 conditions? I'm scared to ask.

7 MR. BALO: Dr. Ellenberg's got to be more
8 specific about what you're trying to ask the company
9 to do, because if you're asking them to do a
10 randomized study, you're basically saying that the
11 study they did currently is not satisfactory. And I
12 think you need to be specific like Dr. Witten said to
13 ask a specific question that you want the company to
14 do, because you're voting on approvable with
15 conditions. So I think that you need more
16 clarification, because I'm really confused on what
17 you're asking. I mean I can't vote, so I'm just
18 asking for the company's sake.

19 DR. JENSEN: Can I ask for one
20 clarification too? Is this like a voluntary thing,
21 you ask patients, "Do you want to be randomized," or
22 is this the company tells people, "You've got to be

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1 randomized"?

2 DR. ELLENBERG: I don't think we do that
3 anymore.

4 (Laughter.)

5 DR. JENSEN: Well, and the only reason I
6 bring it up is that, once again, bringing back
7 reticropasty, we're trying to run a trial now where
8 we ask people to randomize the best medical therapy
9 versus reticropasty, and no one will randomize. So I
10 mean you can ask for it, but I suspect you will get
11 nobody in it or very few people.

12 DR. ELLENBERG: When we make a
13 recommendation, it's a recommendation to FDA, as I
14 understand it, and FDA is left to its own devices -- I
15 didn't mean that.

16 (Laughter.)

17 FDA must negotiate with the sponsor as to
18 feasibility of the recommendation and so to whether or
19 not this is a wise use of resources by the sponsor, as
20 to whether or not it's an ethical approach that is
21 fair to patients, and that I would leave to FDA.

22 The specifics of what I would think is

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1 necessary -- I'm just repeating myself. I don't
2 believe we have a number that we can give to
3 physicians that says we believe the benefit in this
4 population of adjunctive VNS -- the adjunctive VNS
5 approach is the following, plus or minus a number that
6 brings about a small probability into your statement.

7 I don't think that's inconsistent with
8 approving the drug and meeting the standards, as
9 defined, for safety and efficacy. If it's
10 inconsistent, then the Panel should either vote this
11 down or let FDA take this and say, "This is
12 consistent." I can't be more specific than that. And
13 if that doesn't meet the standard, then we need to
14 vote this down.

15 CHAIRPERSON BECKER: And what happens if,
16 as Dr. Jensen mentioned and as my fears are, that you
17 launch this study and no patients opt to randomized
18 into the study, they all opt for the device
19 implantation? What does the FDA do then?

20 DR. ELLENBERG: That's what the FDA has to
21 deal with.

22 (Laughter.)

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1 If we don't think -- if we think that that
2 number is not important, then we vote down this
3 condition. If we think that number is important, then
4 we're saying a best effort attempt to do this is what
5 we're asking for. If the study fails after a bona
6 fide attempt, then I believe -- if FDA accepts our --
7 if we vote this and we approve the global motion and
8 FDA accepts the recommendation for the global motion
9 and accepts the condition, then FDA will work out with
10 the Sponsor what is necessary to go forward to do
11 this, as they would with any other trial for initial
12 approval, and the company will do what FDA says, and
13 it could fail.

14 CHAIRPERSON BECKER: With that, can I just
15 ask for another vote on this particular condition?

16 Everybody in favor of asking the company
17 to perform a Phase IV randomized trial please raise
18 their hands. So Dr. Malone, Dr. Wang, Dr. Fochtman
19 and Dr. Ellenberg.

20 Everybody opposed to this condition? Drs.
21 Jensen, Ortiz and Jayam-Trouth.

22 Everybody abstaining from this vote?

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1 DR. ELLENBERG: Don't you have to vote?

2 CHAIRPERSON BECKER: So I actually hear a
3 -- we're actually having a change in vote. So it's
4 going to be three for, three against and one
5 abstention.

6 DR. ELLENBERG: And you're the deciding
7 vote.

8 CHAIRPERSON BECKER: Yes. Actually, let's
9 have our hands up again for everybody in favor of
10 this. So Dr. Malone, Dr. Wang and Dr. Ellenberg in
11 favor.

12 Everybody opposed? Dr. Jensen, Dr. Ortiz,
13 Dr. Jayam-Trouth.

14 In abstention is Dr. Fochtman.

15 So three for, three against and one
16 abstention.

17 PARTICIPANT: What's your vote?

18 (Laughter.)

19 CHAIRPERSON BECKER: Well, you know, I'm
20 going to vote against this condition, because it seems
21 to me that this really isn't a condition. It's asking
22 for a non-approval. And if we're going with

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1 conditional approval, I'm going to eliminate this
2 condition.

3 Any other conditions that people would
4 like to move to include? Okay.

5 With that, I think we'll vote on the main
6 motion. It's the recommendation of the Panel that the
7 pre-market approval application, P97003, Supplement
8 50, for the Cyberonics VNS System intended for the
9 adjunctive long-term treatment of chronic or recurrent
10 depression for patients who are experiencing a major
11 depressive episode that has not had an adequate
12 response to two or more antidepressive treatments be
13 conditionally approved with the conditions of approval
14 the Panel has just voted on. The initial motion
15 carried four to one and there were two abstentions.

16 So to go through the conditions, if I can
17 remember them and read my writing, Condition 1 was
18 that patients must fail four or more adequate trials
19 of antidepressant therapy. Condition 2 is that the
20 surgeons that are going to implant this device need to
21 be identified for their skills operating within the
22 carotid sheath. Condition 3 is that the clinicians

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1 caring for these patients receive some sort of
2 documentation that they've been trained in setting the
3 device parameters. Condition 4 is that the patients
4 be educated as to the complications of the device and
5 then the need for device removal should they need
6 diagnostic studies.

7 Condition 5 really supplants the last
8 condition that we just voted down, which is a registry
9 that we would like to ask the Sponsor to create to
10 collect further data that will help us identify
11 prognostic factors to determine who responds to VNS
12 stimulation, information about stimulus settings that
13 are effective and further efficacy and safety data.

14 Condition 6 and most of the rest of the
15 conditions have to do with changes in labeling.
16 Condition 6 states that the labeling should be changed
17 to reflect that the 12-month study was really an open
18 label trial and not a randomized controlled trial.
19 Condition 7 states that there should be a change in
20 the language from, "highly statistically significant
21 result," to, "a significant result," with the deletion
22 of the p value. Condition 8 and Condition 10 I'm

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1 going to combine, and that condition would be that the
2 VNS stimulation may be considered for patients with
3 treatment-resistant depression who have failed four or
4 more adequate therapies. Condition 9 is to delete
5 information on blood flow studies following nerve
6 stimulation. And Condition 10 actually we've just
7 dealt with in combination with Condition 8.

8 So with that set of conditions, all in
9 favor of the main motion with the identified
10 conditions of approval please raise their hand. Dr.
11 Ortiz, Dr. Jensen, Dr. Wang, Dr. Fochtman and Dr.
12 Jayam-Trouth.

13 All opposed to the condition for approval
14 -- the conditional approval with the conditions just
15 read please raise your hands?

16 DR. ELLENBERG: Are we only voting on the
17 conditions or --

18 CHAIRPERSON BECKER: No, the whole shebang
19 at this point. Dr. Malone and Dr. Ellenberg.

20 And everybody abstaining from voting,
21 which would be me.

22 So it is the recommendation of the Panel

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1 that the pre-market approval application, P97003,
2 Supplement 50, for the Cyberonics VNS System intended
3 for the adjunctive long-term treatment of chronic or
4 recurrent depression for patients who are experiencing
5 a major depressive episode that has not had an
6 adequate response to two or more antidepressant
7 treatments be conditionally approved with the
8 previously voted upon conditions. The motion carried
9 five to two, and there were zero abstentions.

10 I'm now going to ask each panel member for
11 the reason for his or her voting, starting with Dr.
12 Ellenberg.

13 DR. ELLENBERG: My principal reason for
14 voting against approval is because in this non-
15 randomized comparative study, I don't believe that a
16 standard for efficacy has been met.

17 DR. JAYAM-TROUTH: The reason I'm voting
18 for approval with conditions is that I mean this is a
19 very tough group of patients, and it's difficult to
20 treat them. The death rate is very high, it's almost
21 a terminal type of a condition, more or less, and I
22 think that there's very little that we can offer at

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1 this time, and I think we have shown that this is
2 relatively safe. There have been studies on epilepsy
3 shown that it is efficacious in this group of patients
4 and the efficacy seems to improve over time. So I
5 think that for the reasons I mentioned, I'm voting for
6 approval.

7 DR. FOCHTMANN: I'm also voting for the
8 approval with conditions for the same reasons that
9 although I would have liked to have seen a more
10 rigorous study, I think that there has been evidence
11 shown that this is efficacious in a very, very
12 difficult to treat group of individuals who are
13 suffering a great deal from these conditions. And I
14 think that the safety has similarly been demonstrated.

15 CHAIRPERSON BECKER: Dr. Wang?

16 DR. WANG: I'm voting for this on the
17 basis of mainly the acute Phase D-02 data which
18 supports that there is some efficacy, although albeit
19 not particularly robustly and not on the basis of the
20 2D-04 comparison. And once you exhaust a few
21 reasonably known treatments, there really is nothing
22 else, and what gets used is less supported by the

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1 data. So this is probably an improvement over, say,
2 fourth line, fifth line sort of treatments.

3 DR. JENSEN: I voted for because I feel
4 the safety data meets the criteria for safety, and
5 although it would be nice to have randomized
6 controlled data for the efficacy, I believe this is a
7 difficult patient population. I believe it will be
8 difficult to and perhaps difficult in many ways, not
9 only just doing the trial but also getting centers to
10 agree to do it based upon ethics and IRB issues to
11 actually have a second trial. And I think it should
12 be at least available to this group of patients, and I
13 hope that the registry will collect some of the data
14 if not all of the data that we want to see
15 prospectively.

16 DR. ORTIZ: I'm voting in favor because I
17 feel that treatment-resistant depression does have a
18 very high incidence of suicide. The data was not
19 ideal, but safety I think was established.

20 DR. MALONE: I voted against because I
21 thought it should not have been approved, because I
22 didn't think they demonstrated efficacy.

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1 CHAIRPERSON BECKER: And Ms. Wells and Mr.
2 Balo, any comments that you might have?

3 MR. BALO: A lot has been said, but I
4 really think from the testimony from the patients
5 today it's good to have something to treat this group
6 of patients. I think it's good to have available and
7 let the physician and the patients choose what's right
8 for their condition.

9 CHAIRPERSON BECKER: I'd like to thank the
10 Panel for their deliberations. And, Dr. Witten, do
11 you have any comments?

12 DR. WITTEN: No. I'd just like to thank
13 the Panel.

14 CHAIRPERSON BECKER: Okay. With that,
15 this meeting of the Neurological Devices Panel is
16 adjourned.

17 (Whereupon, at 5:42 p.m. the Meeting of
18 the Neurological Devices Panel was concluded.)
19
20

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